Anxiety in Schizophrenia

Treatment with Pregabalin

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DISSERTATION SUBMITTED 2018

AALBORG UNIVERSITY
DENMARK

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ENGLISH SUMMARY

Background

Anxiety symptoms is common among patients with schizophrenia and pose a large negative impact on patients perceived quality of life, daily functioning and is associated with increased risk of suicide.

The evidence concerning the pharmacological treatment of anxiety in schizophrenia is sparse and rely primarily on treatment guidelines aimed at non-psychotic anxiety disorders. The anxiolytic properties of pregabalin is well established. Based on case reports and smaller case series pregabalin has been suggested as treatment for anxiety in schizophrenia. However, no randomized clinical trials have been conducted to investigate the efficacy of pregabalin in patients with schizophrenia and severe anxiety symptoms.

Increasing numbers of clinical CNS trials fail to separate active drug from placebo. Methodological and statistical problems related to study design and methods of efficacy assessment may be a part of the explanation. Centralized rating in psychometric testing has been suggested as a method to increase accuracy and reduce bias and focus on the psychometric properties of the assessment scales may increase the precision in clinical trials.

Although the pharmacokinetics of pregabalin limits the risk of drug-drug-interactions, case reports have suggested an interaction between pregabalin and the antipsychotic drug clozapine. The mechanism behind this possible interaction remains unknown and has not been investigated systematically. Although, pregabalin is considered well tolerated, case reports and epidemiological studies have suggested an abuse potential of pregabalin, especially among persons with a history of substance abuse. Both the potential DDI with clozapine and the abuse potential may limit the use of pregabalin for the treatment of anxiety in schizophrenia.

Methods

The main study of this thesis (the PACS study) is a randomized double-blinded placebo-controlled trial designed to evaluate the efficacy and safety of pregabalin as add-on treatment for anxiety in patients with schizophrenia by using remote centralized ratings of the Hamilton Anxiety Scale (HAM-A) as primary outcome

(Study I). By using HAM-A ratings from both site-based ratings and remote centralized ratings the validity and scalability of HAM-A_{14} and HAM-A_6 and differences in efficacy estimations was evaluated. Further, "exit-poll" data were used to evaluate the blinding success in the PACS study **(Study II)**. Blood samples, from a subsample of participants in antipsychotic treatment with clozapine, was used to assess the stability of plasma clozapine during concomitant treatment with pregabalin **(Study III)**. A systematic literature search and review of preclinical, clinical and epidemiological data was commenced to evaluate the abuse potential of pregabalin **(Study IV)**.

Overall findings

Pregabalin showed superiority to placebo in reducing anxiety symptom severity as measured by the HAM-A_6. Superiority could not be confirmed on the HAM-A_{14}. Pregabalin was generally well tolerated. Analysis of the statistical properties of the HAM-A_{14} and the HAM-A_6 showed a sufficient scalability of the HAM-A_6 whereas the the HAM-A_{14} showed signs of multidimensionality. The suspected DDI between pregabalin and clozapine could not be confirmed in the analyses of the blood material from the PACS study. Overall, the available literature suggests an important clinical abuse potential of pregabalin and this may be a limitation in the use of pregabalin for the treatment of anxiety in patients with schizophrenia – especially in patients with ongoing or previous substance abuse.

DANSK RESUME

Baggrund

Angst forekommer hyppigt hos personer med skizofreni. Tilstedeværelsen af angstsymptomer har en negativ indvirkning på den oplevede livskvalitet, dagligt funktionsniveau og er forbundet med en øget risiko for selvmord.

Den videnskabelige evidens for farmakologisk behandling af angst ved skizofreni er sparsom og baserer sig primært på guidelines vedrørende behandling af egentlige angstlidelser. Den angstdæmpende effekt af pregabalin er velkendt og pregabalin har på baggrund af kasuistikker været foreslået som behandling af angst hos personer med skizofreni. Indtil videre har der ikke været gennemført større randomiserede kliniske studier med det formål at undersøge effekten af pregabalin til behandling af angst ved skizofreni.

Gennem de seneste år har et stigende antal kliniske studier fejlet i forhold til at kunne påvise effekt af aktive lægemidler i sammenligning med placebo. Metodologiske og statistiske problemstillinger i forbindelse med designet af studierne menes at være en medvirkende årsag hertil. Brug af centraliseret rating er blevet foreslået som en mulighed i forhold til at håndtere nogle af de førnævnte problemstillinger.

En mulig interaktion mellem pregabalin og det antipsykotiske lægemiddel clozapin har været beskrevet i enkelte kasuistikker. Stigende plasmakoncentration af clozapin er observeret efter opstart af samtidig behandling med pregabalin. Det biologiske grundlag for denne mulige interaktion er ikke klarlagt. Yderligere har epidemiologiske studier og flere publicerede kasuistikker peget på et muligt misbrugspotentiale ved pregabalin. Begge disse forhold kan potentielt begrænse brugen af pregabalin som effektiv og sikker behandling af patienter med skizofreni og betydende angstsymptomer.

Metode

Hovedstudiet i denne afhandling undersøger effekten af pregabalin, sammenlignet med placebo, i en gruppe af personer med skizofreni og betydende angstsymptomer **(Studie I)**. På baggrund af data fra centraliseret rating og site-baseret rating undersøges de psykometriske egenskaber af HAM-A_{14} og HAM-A_6, samt forskelle i effektmålinger baseret på de forskellige rating-metoder **(Studie II)**. På baggrund af blodprøve-materiale indsamlet i **Studie I** undersøges stabiliteten af plasma-clozapin

under samtidig behandling med pregabalin **(Studie III)**. I en systematisk gennemgang af publiceret litteratur gives en vurdering af misbrugspotentialet ved pregabalin ud fra prækliniske, kliniske og epidemiologiske data **(Studie IV)**.

Overordnede resultater

Samlet set blev der fundet effekt af pregabalin ved behandling af angst hos patienter med skizofreni, målt på HAM-A_6 skalaen, samt på den psykiske angstfaktor af HAM-A_{14} skalaen. Forskellen mellem placebo og pregabalin var statistisk betydende og effektstørrelsen var moderat. Behandlingen var generelt veltålt. Analyse af HAM-A data viste en større psykometrisk validitet af HAM-A_6, sammenlignet med HAM-A_{14}. Mistanken om en lægemiddelinteraktion mellem pregabalin og clozapin kunne ikke bekræftes ud fra analyserne af det indsamlede blodprøve materiale. I litteraturgennemgangen blev der fundet indicier for et betydende misbrugspotentiale af pregabalin. Dette kan potentielt være en begrænsende faktor i forhold til anvendelsen af pregabalin til behandling af angst ved skizofreni.

LIST OF INCLUDED STUDIES

This PhD thesis is based on three original studies and one systematic review. The results from **Study I** have been published in *Schizophrenia Research* and the results from **Study IV** have been published in *CNS Drugs*. A manuscript based on **Study III** has been recommended for publication in *Pharmacopsychiatry* and is currently under revision. A manuscript based on **Study II** is currently in preparation. Journal articles and manuscripts are appended in this thesis. Some sentences and phrases, mainly pertaining to description of specific methods, statistics and results are exact quotations from the papers and manuscripts below (Appendices I-IV). Most tables and figures are directly copied from the underlying papers and manuscripts. The extracts from the papers and manuscripts employed in this thesis are presented in *italics*. References in extracts refers to the combined reference list in this thesis.

I. **Pregabalin for anxiety in patients with schizophrenia – a randomized, double-blind placebo-controlled study.** *(In press, Schizophrenia Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.09.014).*
Ole Schjerning, Per Damkier, Signe Engelhardt Lykkegaard, Klaus Damgaard Jakobsen and Jimmi Nielsen.
Referred to in text as **Paper I** and referenced as (1)

II. **Use of remote centralized rating versus site-based rating in the PACS study.** *(In preparation).*
Ole Schjerning, Per Bech, Per Damkier, Klaus Damgaard Jakobsen and Jimmi Nielsen.
Referred to in text as **Paper II** and referenced as (2)

III. **The effect of pregabalin on plasma levels of clozapine in patients with schizophrenia – results from a randomized trial.** *(Recommended for publication in Pharmacopsychiatry).*
Ole Schjerning, Klaus Damgaard Jakobsen, Jimmi Nielsen and Per Damkier.
Referred to in text as **Paper III** and referenced as (3)

IV. **Abuse potential of Pregabalin – A Systematic Review.** *(CNS Drugs, 2016, Vol. 30, p. 9-25.)*
Ole Schjerning, Mary Rosenzweig, Anton Pottegård, Per Damkier and Jimmi Nielsen.
Referred to in text as **Paper IV** and referenced as (4)

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACTTION	The Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Network ADR Adverse Drug Reaction
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BI	Blinding Index
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
BZD	Benzodiazepines
CDSS	Calgary Depression Scale for Schizophrenia
CGI-I, CGI-S	Clinical Global Impression – Improvement, Symptoms
CI	Confidence Interval
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPP	Conditioned Place Preference
CR	Centralized Raters
CYP	Cytochrome P450 enzyme
DDI	Drug-Drug Interaction
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
ECG	Electro-Cardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABA	Gamma-Amino-Butyric-Acid
GAD	Generalized Anxiety Disorder
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Scale

ICC	Intraclass Correlation Coefficient
ICD-10	International Classification of Disease – Version 10
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IQR	Interquartile Range
ITT	Intention-To-Treat
LOCF	Last-Observation-Carried-Forward
LSEQ	Leeds Sleep Evaluation Questionnaire
MAH	Marketing Authorization Holder
MAREs	Misuse Abuse Related Events
MSA	Mokken Scale Analysis
OCD	Obsessive Compulsive Disorder
OCS	Obsessive Compulsive Symptoms
PACS	Pregabalin for Anxiety Comorbidity in Schizophrenia
PANSS	Positive and Negative Syndrome Scale
PP	Per Protocol
PSP	Personal and Social Performance
QOL	Quality of Life
RCT	Randomized Clinical Trial
SAES	Scale of Anxiety Evaluation in Schizophrenia
SNRI	Selective serotonin and Noradrenaline Reuptake Inhibitor
SPC	Summary of Product Characteristics
SR	Site-based Rater
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
UKU	Udvalg for Kliniske Undersøgelser
VAS	Visual Analog Scale
WHO	World Health Organization

1. BACKGROUND

ANXIETY IN SCHIZOPHRENIA

Schizophrenia is a severe, often chronic mental disorder affecting approximately 0.5% of the population, with up to 10 % of patients being institutionalized (5). The psychopathology of schizophrenia includes psychotic symptoms, e.g. hallucinations and delusions, negative symptoms, e.g. blunted affect and social withdrawal, disorganization of thoughts and behavior and cognitive impairment (6).

Anxiety is a future-oriented emotional state that is experienced by all humans to varying degree (7). Anxiety is accompanied by a characteristic set of behavioral and physiological responses, experienced as anxiety symptoms, including avoidance, vigilance and arousal, which evolved to protect the individual from danger (8). Anxiety symptoms are conceptualized as anxiety disorders (ADs) when they constitute specified syndromes and are intensive, recurrent, and impede an individual's psychosocial functioning (9).

Anxiety symptoms have long been recognized as a core aspect of schizophrenia (10). However, the diagnostic approach and classification of anxiety in schizophrenia is inconsistent. In the categorical approach to diagnosing psychiatric illnesses in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), anxiety in schizophrenia is diagnosed as comorbid anxiety disorders and not perceived as a core symptom set in schizophrenia (11). It is estimated that up to 40% of patients fulfils the criteria for any anxiety disorders (12), with lifetime prevalence being as high as 70% (13).

In the World Health Organization International Classification of Disease, 10th edition (WHO ICD-10), anxiety symptoms in patients with schizophrenia is not diagnosed, as the ICD-10 system uses a hierarchical approach and disorders lower in the diagnostic hierarchy is not added as comorbidities to the main diagnosis, e.g. schizophrenia. The downside to this approach may be that anxiety symptoms receives less attention than e.g. positive symptoms as clinicians might pay more attention to hallucinations and delusions than the more unspecific anxiety symptoms (14).

The level of anxiety symptoms may not be constant throughout the course of schizophrenia, but rather fluctuating with other symptoms (15). Some studies have found that the severity of acute psychosis is positively correlated with the severity of anxiety symptoms and severity of depressive symptoms. The clinical attention towards the psychotic symptoms may overshadow the presence and importance of

anxiety or depressive symptoms (16). Among patients in post-acute or stable phase of their disorder, severe levels of anxiety in schizophrenia are linked with greater levels of hallucinations, poorer psychosocial functioning lesser hope for the future (17). In a 12-month study examining patients hospitalized due to psychotic relapse, a general lessening of symptoms and a decrease in anxiety symptoms occurred over time, but comorbid anxiety disorder was still present in 47% of patients and 33% fulfilled criteria for more than one anxiety disorder after the psychotic episode had diminished (18).

Anxiety results in increased burden and poorer prognosis of the disease and is associated with increased risk of suicide and sleeping disturbances, and anxiety symptoms are highly associated with quality of life in patients with schizophrenia (19). However, little research has been conducted to address the treatment of anxiety symptoms in this population and clinicians mostly rely on the guidelines for treatment of anxiety disorders in non-psychotic populations.

TREATMENT OF ANXIETY IN SCHIZOPHRENIA

The treatment of anxiety disorders in non-psychotic populations has been well investigated and thorough treatment guidelines exists (20, 21). The most widely used drugs are the selective serotonin and noradrenaline reuptake inhibitors (SSRI and SNRI), certain tricyclic antidepressants (TCA), benzodiazepines (BZD) and anticonvulsants, like pregabalin (20). The use of atypical antipsychotics, either as monotherapy or as augmenting therapy have been investigated in clinical trials with promising results, however, the side effects profile may limit the use in the treatment of anxiety disorders (22).

Antipsychotic drugs remain a cornerstone in the treatment of schizophrenia. The specific effect of antipsychotic drugs on anxiety symptoms, have only been investigated in few studies, mostly case reports or smaller studies with open design (23-25). The evidence does not allow for any clear recommendations so far.

Another reasonable approach is the use of drugs with known anxiolytic effect as add-on or augmenting treatment. However, the evidence remains sparse and the treatment is often leading to unwanted and potentially unsafe polypharmacy (26, 27). As reviewed by Temmingh & Stein (28) and Howells, Kingdon & Baldwin (29), evidence for the use of known anxiolytics is mostly based on existing treatment guidelines for anxiety disorders. A few randomized studies have focused on the use of SSRIs, SNRIs or TCAs for the treatment of anxiety disorders in schizophrenia, mostly concerning the treatment of Obsessive-Compulsive Disorder (OCD) or Obsessive-Compulsive Symptoms (OCS) (30-32).

The anxiolytic effect of BZDs is well-established, and this class of drugs is commonly used as concomitant treatment for patients with schizophrenia (33). Although, BZDs may be acceptable in the treatment of acute anxiety states (34), long-term use is not recommended due to adverse effects, i.e. reduced cognitive functioning and risk of tolerance and dependence (35). Further, the use of BZDs is associated with a marked increase in mortality in patients with schizophrenia (36, 37).

Different novel drugs with known or potential anxiolytic effect have been suggested in the treatment of anxiety in schizophrenia, among these pregabalin (29, 38).

PREGABALIN

Pregabalin is an alkylated analogue of γ-aminobutyric acid (GABA) and binds to the α2δ type 1 protein of the P/Q voltage-dependent calcium channel and reduces the central release of excitatory molecules (39, 40). Pregabalin has been shown effective in the treatment of GAD (41, 42) with effect size comparable to Lorazepam and Venlafaxine (43), but with a more rapid onset of action than venlafaxine and a more favorable cognitive profile compared to BZDs (44). Further, pregabalin has been suggested as treatment of alcohol and BZD dependence (45), both conditions which occur commonly in patients with schizophrenia (46).

Based on case reports and smaller case series, pregabalin has been suggested as "off label" add-on treatment for anxiety in schizophrenia (47, 48). In some cases, treatment with pregabalin resulted in a reduction of both anxiety symptoms, positive and negative symptoms and enabled a reduction in the use of benzodiazepines (48). However, the evidence for the use of pregabalin in the treatment of anxiety in schizophrenia remain sparse and no randomized studies have been conducted so far.

The dose range of pregabalin is 150-600 mg per day, given in either two or three divided doses. In healthy volunteers, pregabalin is rapidly and well absorbed with peak plasma concentrations occurring 1.3 hours (h) after oral administration and with an absolute bioavailability of approximately 90% (49). Pregabalin does not bind to plasma proteins. The apparent volume of distribution following oral administration is approximately 0.5 L/kg.

Metabolism of pregabalin is negligible as most of the drug is excreted unchanged in the urine with a mean elimination half-life of 6.3 h in subjects with normal renal function. Pregabalin plasma clearance is directly proportional to creatinine

clearance, but independent of sex, race, age, female hormonal status, daily dose and dosing regimen (49, 50). Dosage reduction should be considered in patients with impaired renal function (50).

Although, treatment with pregabalin generally is considered well tolerated, the use of pregabalin for the treatment of anxiety in schizophrenia may be problematic. Pregabalin added to clozapine treatment has been associated with increases in plasma levels of clozapine (51-53). Clozapine may cause several dose dependent side-effects such as dizziness, constipation and seizures (54) and several serious drug-drug interactions involving clozapine have been described, with some of them being potentially fatal (55, 56). The mechanism for the potential pharmacokinetic interaction between pregabalin and clozapine remains unclear and a biological plausible explanation has not been found.

Abuse and misuse of pregabalin has been described in case reports and epidemiologic studies (57-59), and the European Summary of Product characteristics (SPC) holds a specific warning on the abuse potential of pregabalin (60). The abuse potential of pregabalin could be a limiting factor for the use of pregabalin in patients with schizophrenia.

ASSESSMENT OF ANXIETY IN SCHIZOPHRENIA

Accurate assessment and diagnosing of anxiety in schizophrenia is challenging. Anxiety symptoms may be a pathophysiological consequence of medical conditions like endocrine disorders, cardio-pulmonary disorders or related to substance abuse (9). Adverse effects from ongiong psychopharmacological treatment, e.g. akathisia, may mimic somatic manifestations of anxiety (28, 61). Thorough investigation of medical history, physical examination, blood testing and electrocardiography may be nescessary in the differential diagnosing of anxiety symptoms.

When assessing anxiety severity in schizophrenia it is important to consider the overlap between positive and negative symptoms, symptoms of depression and the stage of the illness (acute psychosis or chronic stage). Severity of depressive symptoms can be evaluated with the Calgary Depression Scale for Schizophrenia (CDSS) (62). This scale is especially developed for assessing depression in schizophrenia and a comparison to the Hamilton Depression Scale (HAM-D) found the CDSS to be less confounded by positive and negative symptoms (63).

The Positive and Negative Syndrome Scale (PANSS) (64) is one of the most widely used assessment scales for measuring positive and negative symptoms of schizophrenia (65). PANSS is a clinician administered scale, based on a structured clinical interview. The full scale consists of 30 items, each item is scored on a 7-

point scale with increasing severity of psychopathology, "1" equals symptom absent and "7" symptom being extreme, thus the theoretical range is 30 to 210 (64). The composite scale consists of three subscales (positive symptoms, negative symptoms and general psychopathology) based on the hypothesis that positive and negative symptoms constitute the main dimensions of schizophrenia (66, 67). The psychometric properties and clinical validity of the two-factor model in the PANSS scale has been questioned and other factor models have been suggested (65, 68, 69). In the five-factor model suggested by Lindenmayer et al (70), *Factor 5* covers the dimension of *Anxiety/Depression* based on four items from the general psychopathology subscale, *anxiety (G2), guilt (G3), tension (G4) and depression (G6)*.

Whether anxiety in schizophrenia differ qualitatively from conventional anxiety disorders remains unclear (11). However, anxiety in schizophrenia may possess specific features, as being more silent and intense compared to anxiety disorders or anxiety in mood disorders, it may be accompanied by psychomotor disturbances such as agitation and it has less somatic impact (71). A novel composite rating scale (SAES), using items from both the PANSS scale, the Brief Psychiatric Rating Scale (BPRS) and the Hamilton Anxiety Rating Scale (HAM-A) has been developed and validated in patients with schizophrenia (71), but the SAES needs further evaluation in clinical trials regarding the psychometric properties. Until further research has been conducted, the use of assessment scales designed for other conditions must be used.

THE HAMILTON ANXIETY SCALE

The Hamilton Anxiety Rating Scale (HAM-A) (72) is one of the most widely used rating scales to assess severity of anxiety symptoms. It was originally developed to assess symptom severity in anxiety neurosis but have been used in other psychiatric conditions as well. The HAM-A has been used in clinical studies for the assessment of anxiety in schizophrenia and found to have acceptable level of internal consistency (73).

In placebo-controlled, randomized clinical trials to evaluate the anxiolytic effect of medication the HAM-A (72) remains the most widely used outcome measure. The HAM-A is clinician administered, typically based on a semi-structured interview. The original scale, developed in 1959 by Max Hamilton, contained 13 items (74). Later the scale was expanded to 14 items (72), which is now the predominant version of the scale. The individual items are scored on a 5-point scale (*0 = "not present" to 4 = "maximum degree"*) given the full HAM-A_{14} a theoretical range from 0 to 56. The HAM-A has a high interrater reliability, even with less experienced raters (75). The items of the HAM-A_{14} is presented in *Table 1*.

By factor analysis, Hamilton confirmed multidimensionality of the HAM-A_{14} by identifying to factors, a psychic anxiety factor (items 1 to 6 and item 14) and a somatic anxiety factor (items 7 to 13) (72). The usefulness of these two factors for discriminating between differential treatment responses has been shown in randomized clinical trial investigating the efficacy of different anxiolytic drugs.

Over the past decades, the antidepressants have been shown to be superior to benzodiazepines, e.g. diazepam, in placebo-controlled trials with the HAM-A. Thus, one of the first (76) demonstrated that imipramine was significantly superior to diazepam especially on the psychic anxiety factor in the HAM-A. The SSRIs showed superiority to placebo on the psychic factor of the HAM-A (77, 78). As a primary anxiolytic drug pregabalin was approved in the treatment of generalized anxiety disorder by demonstrating significant superiority over placebo and benzodiazepines on the psychic factor of the HAM-A (79).

Table 1 *– HAM-A_{14} (*items included in the HAM-A_6) (adapted from Gjerris et al (75)).*

Item number	Symptom
1*	Anxious mood
2*	Tension
3*	Fears
4	Insomnia
5*	Difficulties in concentration and memory
6	Depressed mood
7*	General somatic symptoms (Muscular tension)
8	General somatic symptoms (sensory)
9	Cardiovascular symptoms
10	Respiratory symptoms
11	Gastrointestinal symptoms
12	Genito-urinary symptoms
13	Other autonomic symptoms
14*	Behavior during interview

A shorter version of the scale, HAM-A_6, including the items of anxious mood, tension, fears, difficulty in concentration, muscular tension, and anxious behavior during interview (items 1, 2, 3, 5, 7 and 14), has been found to cover the core items

for anxiety state severity in GAD (80). Bech (43) re-analyzed placebo-controlled pregabalin trials in GAD using the HAM-A_6 and confirmed that pregabalin was superior to placebo on the HAM-A_6 (43).

METHODOLOGICAL ISSUES IN EFFICACY TRIALS INVOLVING PSYCHOTROPICS

In the recent years, a growing number of trials have failed to show difference between active treatment and placebo (81, 82). This observation may partly be attributed to an apparent increase in placebo response over the years (83). Several factors may be responsible for this change and for example increased clinical attention during study visits may contribute (83). Another issue is the use of quantitative psychometric testing for inclusion criteria and outcome assessment resulting in inflated baseline values, a phenomenon known as the therapeutic contrast effect or "baseline inflation", where raters might tend to give a too high score at baseline to ensure that the patient fulfils the inclusion criteria (83). Placebo group regress towards "true values" resulting in a falsely high placebo response.

Another challenge related to the use of psychometric rating scales is the psychometric and statistical properties of the scales. To perform sufficiently a psychometric scale must be uni-dimensional, meaning that responses to individual items are explained by a common latent trait, i.e. anxiety. Further, individual items must be locally independent meaning that the relationship between items are explained by the latent trait and not by response to other items. The monotonicity of a scale means that the responses to a given item is a non-decreasing function of the latent trait. The Mokken Scale Analysis (MSA) is a method of testing whether a scale fulfills these assumptions (84).

Concealment of treatment allocation and maintaining blinding is essential to the validity of clinical trials. However, concurrent rating of both effect parameters and adverse effects may cause functional un-blinding of assessors (85). Use of centralized rating has been suggested as a method of complying with some of the problems concerning the use of psychometric testing in order to make more precise ratings in efficacy studies (86). Different setups and methods have been described in previous studies, i.e. use of video conferencing or teleconferencing making ratings in real time (87, 88).

CENTRALIZED RATING OF THE HAMILTON ANXIETY SCALE

The high inter-rater reliability of the HAM-A has contributed to the widely use as outcome measure in trials investigating the anxiolytic effect of drugs (89). However, Shen et al (88) have introduced the use of remote centralized raters to take into account some of the constant errors related to the site-based raters which are in operation in the traditional clinical trials, such as the therapeutic contrast effect (90, 91). This constant error is not covered by the evaluation of the inter-rater reliability.

The remote centralized raters are blinded to the order of the assessment visits in the study and to the protocol. They have only access to the video-recorded interviews with the participating patients (88). It is the site-based raters who are responsible for the management of the study performing all the protocol-related clinical assessments. The knowledge of typical adverse effects or assessment number may result in functional un-blinding of site-based raters and thereby biasing the assessments. Because Shen et al (88) demonstrated that patients with schizophrenia are willing and able to participate in clinical trials using remote centralized raters with access to video-taped interviews, remote centralized rating was used as a precautionary method of blinding in the PACS-study.

2. AIMS

STUDY I (PACS STUDY)

The aims of this study were to evaluate the efficacy, tolerability and safety of pregabalin as add-on treatment for anxiety in patients with schizophrenia. The study was conducted as a randomized, placebo-controlled, double-blinded clinical trial. The HAM-A was used to quantify severity of anxiety symptoms and to measure treatment response. Outcome measures were assessed at baseline, after 4 weeks and after 8 weeks of treatment.

STUDY II

The aim for this study was to describe the method of remote centralized ratings used in the PACS Study. The scalability and statistical properties of the $HAM\text{-}A_{14}$ and the $HAM\text{-}A_{6}$ was analyzed using data from both the centralized ratings and site-based ratings. Differences in efficacy assessments between the different methods of rating was also assessed.

STUDY III

The aim for this study was to explore the stability of plasma clozapine concentrations before and after initiation of pregabalin in patients in antipsychotic treatment with clozapine. This study was conducted as a prospective observational study based on blood samples obtained from the PACS Study.

STUDY IV

The aim for this study was to evaluate the abuse potential of pregabalin through a systematic review of preclinical, clinical and epidemiologic studies.

3. METHODS

STUDY I (PACS STUDY)

The PACS study was an investigator-initiated study designed as a randomized, double-blinded, placebo-controlled study. Patients were recruited from all five regions of Denmark. First patient was included at 5th of March 2012 and last patient ended the study at 15th of August 2016 (1). The study was ended before sample size goal was met due to failure in accessing eligible patients (1). The methods used in **Study I** (PACS study) is described in detail in the appended **Paper I** (1).

PARTICIPANTS

In- and exclusion criteria for **Study I** is described in detail in the appended **Paper I** (1). A brief overview is provided below:

Inclusion criteria:

- Age 18 to 65 years.
- Diagnosis of schizophrenia[1] (ICD-10 F20.0 to F20.3 or F20.9).
- No changes in primary psychopharmacologic treatment (antipsychotics, antidepressants and sedatives) for at least 4 weeks.
- HAM-A_{14} > 15 (site-based ratings).
- PANSS total score < 70.
- CDSS score < 10.

Exclusion criteria:

- Significant substance abuse.
- Dysregulated diabetes.
- For Females - pregnancy or breastfeeding.
- Legal coercion according to the Danish mental health act.
- Suicidal ideation.

[1] Schizophrenia diagnoses were verified by the investigator, either by review of psychiatric charts or by systematic diagnostic interviews.

RANDOMIZATION AND STUDY INTERVENTIONS

Patients were randomized 1:1 to either pregabalin or placebo. A flexible dosage regime was used – with dosages between 150 mg/d and 600 mg/d depending on patient's subjective anxiolytic effect and experience of adverse effects (1). Details concerning study interventions and the procedures of randomization and concealment of study medication is described in further details in the appended **Paper I** (1).

PRIMARY AND SECONDARY OUTCOMES

Primary outcome was change in anxiety symptom severity as measured by the HAM-A (1). Efficacy outcome was based on the centralized ratings and assessed as the difference between baseline ratings and ratings after 4 and 8 weeks of treatment (1). Analyses were made for the full HAM-A_{14} scale, the HAM-A_6 and the psychic and somatic anxiety factor of the HAM-A_{14} (1). Procedures for centralized rating is described in greater detail in the appended **Paper II** (2). Secondary outcomes of **Study I** is described in detail in the appended **Paper I** (1) and a brief overview of the ratings scales used is provided below:

Psychopathology:

- Positive and Negative Syndrome Scale (PANSS) (64)
- Clinical Global Impression – Severity Scale (CGI-S) (92)
- Clinical Global Impression - Improvement Scale (CGI-I) (92)

Quality of life:

- WHO Quality of Life instrument (WHOQOL-BREF) (93).

Quality of sleep:

- Leeds Sleep Evaluation Questionnaire (LSEQ) (94)

Functioning:

- Personal and Social Performance Scale (PSP) (95).

Tolerability:

- Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (96)

Sedation:

- Visual Analog Scale (VAS)

Akathisia:

- Barnes Akathisia Rating Scale (BARS) (97)

Cognitive functioning:

- Brief Assessment of Cognition in Schizophrenia (BACS) (98).

STUDY II

HAM-A INTERVIEWS AND PROCEDURES OF CENTRALIZED RATING

This study was based on the HAM-A interviews performed under the PACS study (Study I). Both remote centralized ratings and site-based ratings were analyzed. Comparisons were made between the two methods of rating in respect to baseline values and differences in efficacy outcomes (2). A detailed description of the procedures concerning HAM-A interviews and the remote centralized ratings are presented in the appended **Paper II** (2).

ASSESSMENT OF BLINDING

End-of-trial questions to both study participants and site-based raters about what treatment they thought the participant had been allocated to was used in the assessment of blinding success (2). Bang's Blinding Index (BI) (99) were calculated for both study participants and site-based raters. The method used for assessment of blinding success in the PACS study is described in detail in the appended **Paper II** (2).

THE MOKKEN SCALE ANALYSIS

The non-parametric item response theory model developed by Mokken (84) was used to assess the scalability of the HAM-A_{14} and the HAM-A_6. According to this model the coefficient of homogeneity is considered as an expression of the extent to which the individual items in the scale can be rank-ordered by their locations on the underlying dimension of anxiety severity (100). Data from the centralized ratings was used (2). A detailed description of the Mokken scale analysis is provided in the appended **Paper II** (2).

STUDY III

STUDY DESIGN AND PARTICIPANTS

The stability of plasma clozapine during concomitant treatment with pregabalin was evaluated in an observational prospective study design using blood material from the PACS study. Of the total 54 participants in the PACS study, 23 received treatment with clozapine. Blood samples from baseline and at least one of the following two assessments were available for 15 patients. Eight had been allocated to treatment with pregabalin and 7 to placebo (3).

SAMPLE HANDLING AND LABORATORY ANALYSIS

The procedures of sample handling and laboratory analyses performed in **Study III** is described in detail in the appended **Paper III** (3). Blood samples were drawn in the morning and before any morning dosage of clozapine. Participants were instructed to be fasting and not to smoke or drink caffeine containing beverages before blood samples were obtained. Full blood samples were frozen at -80°C until batch analysis. Analyses of plasma clozapine concentration were performed on the 9th of May 2017.

STUDY IV

LITERATURE SEARCH

Study IV was conducted as a systematic review of preclinical, clinical and epidemiological studies concerning pregabalin. Pubmed, Embase and the websites of the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA) were searched using the search term “pregabalin”. The search strategy and selection processes are described in detail in the appended **Paper IV** (4).

4. STATISTICAL METHODS

SAMPLE SIZE ESTIMATION

The details of sample size estimation in **Study I** is described in **Paper I** (1):

"Power calculation was made using STATA 11 Corp. The assumptions were that mean baseline HAM-A14 was 23 ± 9. A clinically relevant change was a 5-point improvement and mean endpoint HAM-A14 was 18 ± 6. With these assumptions, a power of 80% would require 25 patients in each treatment group. A sample size of 35 in each treatment group was chosen to keep sufficient power with a drop-out rate of up to 30%."

DATA HANDLING

The procedures for data handling in the PACS study is described in detail in **Paper I** (1):

"All data collected in the PACS study was entered in EPI-data using double entry by two different persons. Entry-files were compared electronically to avoid typing errors. Statistical analyses were performed in STATA version 14 (StataCorp. 2015. Stata Statistical software: Release 14. College Station, Texas, USA). Primary analysis was Intention-To-Treat (ITT) and secondarily as per protocol (PP). Missing data in the ITT-analysis was replaced as "Last Observation Carried Forward" (LOCF) and all participants receiving at least one dose of treatment medication was included in the ITT analysis. In the PP analysis, patients with a compliance <70% were excluded and missing data was not replaced."

STATISTICAL ANALYSES

Mean (integer) values of ratings from all three raters were used in the statistical analyses on the HAM-A data from centralized ratings. The statistical methods used in the PACS study is described in **Paper I** (1):

"Data were assessed for normality using visual inspection. Logarithmic transformation was used when possible for variables not normally distributed. When transformation was not possible or not sufficient, data was tested with the Wilcoxon rank sum test. Effect size was estimated as Cohen's d. For the main

analysis, mean differences and corresponding confidence intervals were estimated; the corresponding p-values were calculated using two-sided independent samples t-tests. Comparison of categorical data was made using the Fishers' Exact test. For explorative analyses (specific adverse reactions) and explorative comparisons where estimates of differences could not be computed, we adopted a Bonferroni corrected significance level of < 0.001."

In **Study II**, interrater agreement for the three centralized raters was estimated as intra-class correlation coefficients using a two-way fixed effects model measuring absolute agreement on average scores (*ICC (3, k), absolute*) (2). In the Mokken Scale Analysis, *Loevingers coefficient of homogeneity* was calculated for the HAM-A_{14} and the HAM-A_6 on ITT data from both the centralized ratings and the site-based ratings (2). All statistical analyses in were made in STATA version 14 (StataCorp. 2015. Stata Statistical software: Release 14. College Station, Texas, USA). Add-on software packages was used for the calculations of Loevingers coefficient of homogeneity and Bangs Blinding Index (101).

In **Study III**, change in plasma clozapine between baseline and each of the following assessments were calculated for each treatment group (3). Hypothesis testing on baseline concentration and concentration after 4 and 8 weeks of treatment were made using the Wilcoxon signed-rank test (3).

5. ETHICAL CONSIDERATIONS

The PACS study were performed in accordance with the ICH-CGP guidelines and the Declaration of Helsinki (1). All participants gave their informed written consent to participation (1). Participants consent to the video recording and use of HAM-A interviews in the centralized rating procedures (2) and the collection of blood material for later analyses were given separately (3). The Local Ethics Committee, the Danish Health Authority and the Danish Data Protection Agency approved the PACS study protocol (1). The collection of blood material for analysis of plasma levels of clozapine was approved by the Danish Health Authority, Danish Data Protection Agency and the Local Ethics Committee as an amendment to the original PACS study protocol (3).

6. RESULTS

STUDY I

PARTICIPANTS FLOW

A CONSORT diagram of participants flow through **Study I** is shown in *Figure 1 (Originally presented as Figure 1 in Paper I)* (1).

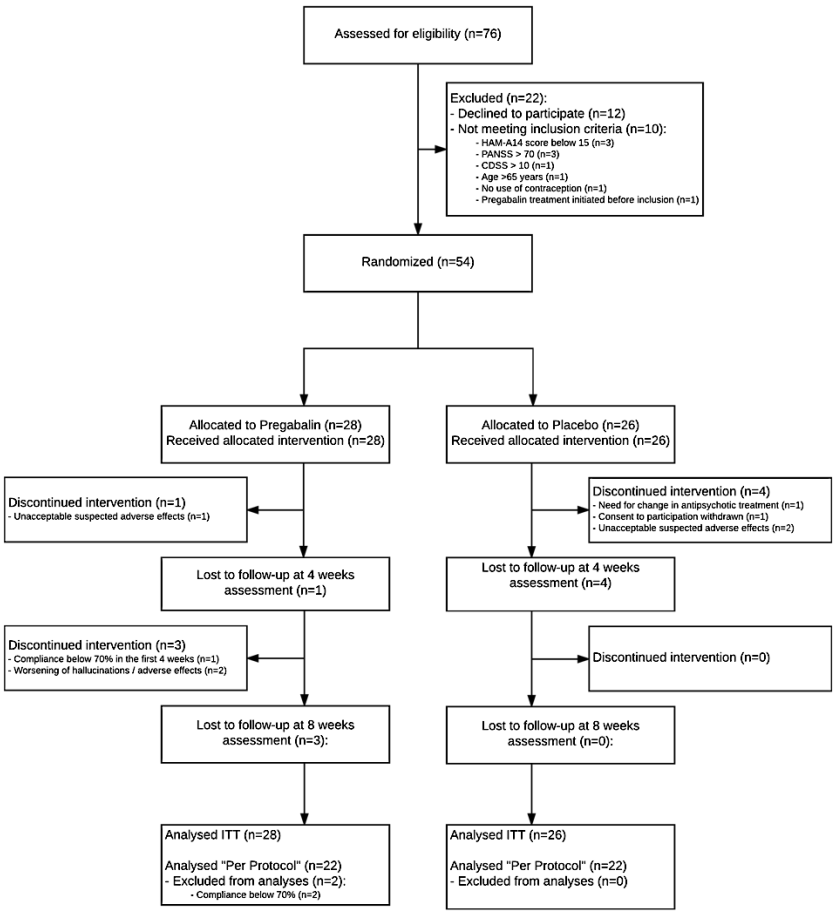

Figure 1 – CONSORT Diagram

BASELINE DATA

Baseline demographics and clinical characteristics for each treatment group are summarized in *Table 2* and *Table 3* (*originally presented as Table 1 in* **Paper I**) (1).

OUTCOMES AND ESTIMATION

Outcomes and estimations of the Intention-to-treat analyses of the HAM-A data is originally presented in **Paper I** (1). An overview of the results is shown in *Table 4* (*originally presented as Table 2 in* **Paper I**) (1). No substantial differences were seen in the ITT analyses compared to the PP analyses (1). Secondary outcomes of the PACS study are originally presented in **Paper I** (1) and data is presented in summary in *Table* 5 (originally Table 3 in **Paper I**) (1). Some patients showed inability to withstand the full test program of the PACS study. As a result, the numbers analyzed for secondary parameters vary. Baseline LSEQ was missing or incomplete for 7 patients. Baseline BACS was missing for 1 patient. Data from these patients are not included in neither ITT or per protocol analyses.

ADVERSE EVENTS

Adverse effects occurring during the PACS study are originally presented in **Paper I** (1). Data from the UKU ratings are summarized in *Table 6* (*originally presented as Table 4 in* **Paper I**) (1). Only patients with at least one follow-up assessment were included in the analysis. In total, UKU data for 47 patients (17 females and 30 males) were included in the assessment of adverse effects (1). A further presentation of data on change in body weight and adverse effects not covered by the UKU scale is presented in the appended **Paper I** (1).

Table 2 – Baseline demographics and clinical characteristics

	Placebo		Pregabalin	
Variable	**Mean**	**SD**	**Mean**	**SD**
- Age (years)	43	10	38	12
- Body weight (kg)	91.7	17.4	84.0	18.9
- Height (cm)	175	10.8	175	10.4
- Systolic blood pressure (mmHg)	123.5	11.2	122.3	10.2
- Diastolic blood pressure (mmHg)	81.8	7.2	81.1	7.0
Laboratory test results				
- P-Creatinine (µmol/l)	83.9	11.8	81.4	12.4
- QTc (ms)	426.8	29.0	423.5	25.6
- Heart rate (min^{-1})	74.3	20.2	81.4	19.0
Psychometrics				
- CDSS (total score)	3.8	2.7	4.3	2.6
Variable	**N**	**%**	**N**	**%**
Sex				
- Male	19	73	17	61
- Female	7	27	11	39
Schizophrenia subtype				
- Paranoid (F20.0)	22	85	22	78
- Undifferentiated (F20.3)	-	-	3	11
- Unspecified (F20.9)	4	15	3	11
Housing situation				
- Independent	18	69	19	68
- Institutionalized	7	27	9	32
- Hospitalized	1	4	-	-

Table 3 – Treatment characteristics. (*Dosage per injection was divided by the number of days between each injection.)

	Placebo group (n=26)		Pregabalin group (n=28)	
Treatment characteristics	**N**	**Mean daily dosage (mg)**	**N**	**Mean daily dosage (mg)**
Oral Antipsychotics				
- Clozapine	10	379	13	425
- Olanzapine	6	24.2	2	20
- Quetiapine	5	395	6	491.7
- Chlorprothixen	2	165	2	25
- Amisulpride	1	300	2	550
- Risperidone	-	-	2	2.5
- Aripiprazole	4	17.5	7	21.4
- Paliperidone	1	150	-	-
- Sertindole	1	16	-	-
LAI Antipsychotics*				
- Olanzapine	1	28.9	-	-
- Flupentixole	-	-	1	7.1
- Risperidone	1	2.7	3	3.3
- Paliperidone	1	5.4	1	6.3
- Aripiprazole	1	14.3	3	14.0
Hypnotics				
- Clonazepam	4	1.95	3	0.83
- Oxazepam	2	22.5	1	15
- Alprazolam	1	0.3	-	-
- Zopiclone	4	7.5	2	5.65
- Zolpidem	2	10	-	-
- Hydroxyzine	-	-	1	50
- Promethazine	1	25	-	-
Antidepressants				
- Amitriptyline	1	125	-	-
- Fluoxetine	1	20	-	-
- Citalopram	3	33.3	3	33.3
- Paroxetine	1	40	-	-
- Sertraline	6	112.5	5	120
- Escitalopram	1	20	3	20
- Mirtazapine	1	30	2	37.5
- Venlafaxine	1	225	2	187.5

Table 4 - Numbers analyzed: placebo, n=26 and pregabalin, n=28. Comparisons made with two-sample independent t-tests. Theoretical range for HAM-A14 total (0 to 56), HAM-A6 (0 to 24) and HAM-A (psychic and somatic factors) (0 to 32).

	Score at Baseline				**Change after 8 weeks of treatment**							
	Placebo		**Pregabalin**		**Placebo**		**Pregabalin**		**Difference between**			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Effect size**	**P**
HAM-A_{14}	22.2	5.9	22.4	4.7	- 3.4	-5.1 to -1.7	-6	-8.9 to -3.0	2.6	-0.8 to 5.9	0.42	0.13
HAM-A_6	10.6	2.8	10.8	2.0	-1.0	-2.2 to 0.1	-3.3	-4.7 to -2.0	2.3	0.6 to 4.0	0.72	0.01
Psychic factor	12.8	3.3	13.0	3.0	-1.6	-3.0 to -0.2	-4.1	-6.0 to -2.1	2.5	0.1 to 4.9	0.57	0.04
Somatic factor	9.5	3.8	9.5	3.1	-1.8	-2.9 to -0.7	-2.1	-3.5 to -0.7	0.3	-1.5 to 2.0	0.08	0.76

Table 5 - Secondary outcome measures. Intention-To-Treat analyses. Numbers analyzed; [1](Placebo n=26, pregabalin n=28), [2](placebo n=25, pregabalin n=28), [3](Placebo n=22, pregabalin n=27), [4](placebo n=21, pregabalin n=26).

	Value at baseline				Change after 8 weeks of treatment						
	Placebo		Pregabalin		Placebo		Pregabalin		Difference between groups		
Outcome variable	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	Mean	95% CI	P
PANSS Total[1]	57.2	8.7	56.8	6.8	-1.2	-3.5 to 1.1	-5.0	-8.3 to -1.7	3.8	-0.1 to 7.7	0.05
PANSS Positive[1]	14.0	3.2	14.5	3.6	0	-1.0 to 1.1	-0.64	-1.9 to 0.6	0.7	-0.9 to 2.3	0.47
PANSS Negative[1]	13.0	4.3	13.4	4.8	0	-1.0 to 1.0	-1.0	-2.4 to 0.4	1.0	-0.7 to 2.7	0.24
PANSS General[1]	30.2	4.4	28.9	3.5	-1.2	-2.4 to 0	-3.4	-5.6 to -1.2	2.1	-0.3 to 4.6	0.07
PANSS Anxiety/Depression[1]	12.8	2.2	12.5	2.4	-1.0	-1.8 to -0.3	-2.7	-4.2 to -1.2	1.7	0 to 3.3	0.05
BACS composite score[2]	32.7	8.5	32.9	6.4	2.5	0.8 to 4.3	-0.2	-2.2 to 1.8	2.8	0.1 to 5.4	0.1
VAS Sedation[3]	56.3	20.0	52.6	23.5	-3	-12.9 to 7	1.7	-8.4 to 11.9	4.7	-9.3 to 18.7	0.5
WHO-QOL – Overall QOL[3]	44.3	17.6	43.5	20.3	6.3	1.0 to 11.6	12	4.0 to 20.1	5.7	3.7 to 15.2	0.22
WHO-QOL – Physical Health[3]	58	15.9	50.5	13.1	1	-4.6 to 5.9	10	6.3 to 13.6	9	3.3 to 15.4	<0.01
WHO-QOL – Psychological[3]	37.6	15.9	35.2	14.3	6	1.2 to 9.8	13	5.5 to 19.6	7	1.1 to 15.1	0.09
WHO-QOL – Environment[3]	51.7	13.3	54.2	16.5	-1	-5 to 3	0	-4 to 4	1	-4 to 7	0.68
	Placebo		Pregabalin		Placebo		Pregabalin		Difference between groups		
Outcome variable	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median		P
WHO-QOL – Soc. relationships[3]	64.5	50 to 72	56	50 to 66	0	-8 to 6	6	-2 to 10	6		0.20
LSEQ – Getting-to-sleep[4]	154	134 to 181	150	120 to 157	-2	-33 to 19	13	0 to 39	15		0.01
LSEQ – Quality-of-sleep[4]	99	74 to 118	86	69 to 100	1	-7 to 20	6	0 to 48	5		0.06
LSEQ – AFS[4]	100	75 to 102	100	56 to 129	0	-9 to 14	0	-35 to 19	0		0.97
LSEQ – BFW[4]	133	103 to 152	132	76 to 159	4	-11 to 30	0	-24 to 45	4		0.68
CGI-S[1]	4	4 to 5	4	4 to 5	0	0 to 0	0	0 to 0	0		0.51
PSP[2]	47	38 to 49	47	44 to 50	0	-3 to 3	-1	-3 to 4	1		0.79
BARS Total[1]	2	0 to 2	1	0 to 3	0	0 to 0	0	-2 to 0	0		0.43
BARS Global Assessment[1]	1	0 to 1	1	0 to 2	0	0 to 0	0	-1 to 0	0		0.46

Table 4 - Total number of patients included in analysis of adverse effects based on the UKU scale: 47 [1]Females (n=17), [2]Males (n=30)

	Total		Placebo		Pregabalin		Fisher's exact
	N	**%**	**N**	**%**	**N**	**%**	***P***
Concentration difficulties	7	15	3	14	4	16	>0.99
Increased fatigability	15	32	6	27	9	36	0.55
Sedation	9	19	4	18	5	20	>0.99
Failing memory	11	23	5	23	6	24	>0.99
Depression	14	30	9	41	5	20	0.20
Tension	8	17	4	18	4	16	>0.99
Increased duration of sleep	17	36	2	9	15	60	**0.001**
Reduced duration of sleep	5	11	3	14	2	8	0.65
Increased dream activity	9	19	3	14	6	24	0.47
Emotional indifference	6	13	2	9	4	16	0.67
Dystonia	2	4	0	0	2	8	0.49
Rigidity	3	6	0	0	3	12	0.24
Hypokinesia / Akinesia	3	6	0	0	3	12	0.24
Hyperkinesia	6	13	1	5	5	20	0.19
Tremor	6	13	3	14	3	12	>0.99
Akathisia	10	21	3	14	7	28	0.30
Epileptic seizures	2	4	0	0	2	8	0.49
Paresthesia	5	11	2	9	3	12	>0.99
Accommodation disturbances	6	13	1	5	5	20	0.19
Increased salivation	7	15	2	9	5	20	0.42
Dryness of mouth	9	19	5	23	4	16	0.72
Nausea / Vomiting	11	23	6	27	5	20	0.73
Diarrhea	10	21	4	18	6	24	0.73
Constipation	6	13	3	14	3	12	>0.99
Micturition Disturbances	9	19	4	18	5	20	>0.99
Polyuria / Polydipsia	11	23	2	9	9	36	**0.04**
Orthostatic dizziness	13	28	7	32	6	24	0.75
Palpitations / Tachycardia	9	19	4	18	5	20	>0.99
Increased tendency to sweating	3	6	1	5	2	8	>0.99
Rash	4	9	1	5	3	12	0.61
Pruritus	3	6	1	5	2	8	>0.99
Photosensitivity	3	6	0	0	3	12	0.24
Increased pigmentation	4	9	0	0	4	16	0.11
Weight gain	22	47	6	27	16	64	**0.02**
Weight loss	10	21	7	32	3	12	0.15
Menorrhagia[1]	5	29	2	33	3	27	>0.99
Amenorrhea[1]	6	35	1	17	5	46	0.33
Galactorrhea[1]	4	24	2	33	2	18	0.58
Gynecomastia[2]	1	3	0	0	1	7	0.47
Increased sexual desire	2	4	0	0	2	8	0.49
Diminished sexual desire	8	17	2	9	6	24	0.25
Erectile dysfunction[2]	6	20	2	13	4	29	0.38
Ejaculatory dysfunction[2]	5	17	1	6	4	29	0.16
Orgasmic dysfunction	10	21	3	14	7	28	0.30
Dry vagina[1]	2	12	0	0	2	18	0.52
Headache	12	26	6	27	6	24	>0.99

STUDY II

CENTRALIZED RATINGS

A total of 149 HAM-A interviews were available for centralized rating and the rating procedures started on July 1st, 2016 and ended September 30th, 2016 (2).

BLINDING OUTCOMES

Data from the analysis of blinding success is presented in *Table 7* (*originally presented as Table 1 in* **Paper II**) (2).

Table 5 - Assessment of blinding success.

	Study participants' Answer, No.				
Intervention	**Pregabalin**	**Placebo**	**Do Not Know**	**Total**	**Data missing**
Pregabalin	14	8	2	24	4
Placebo	13	12	0	25	1
Total	**27**	**20**	**2**	**49**	**5**
Bangs Blinding index: **Study participants allocated to pregabalin:** 0.25 (95% CI -0.06 to 0.56) **Study participants allocated to placebo:** -0.04 (95% CI -0.37 to 0.29)					
	Site-based raters' Answer, No.				
Intervention	**Pregabalin**	**Placebo**	**Do Not Know**	**Total**	**Data missing**
Pregabalin	13	10	1	24	4
Placebo	4	18	1	23	3
Total	**17**	**28**	**2**	**47**	**7**
Bangs Blinding index: **Study participants allocated to pregabalin:** 0.13 (95% CI -0.2 to 0.45) **Study participants allocated to placebo:** 0.61 (95% CI 0.35 to 0.87)					

DIFFERENCES IN RATINGS – SITE-BASED VERSUS CENTRALIZED RATINGS

Mean ratings over time for each treatment group is presented graphically in *Figure 2 (originally presented as Figure 1 in* **Paper II***)* (2) and differences in baseline values and effect sizes after 8 weeks of treatment is presented in *Table 8 (originally presented as Table 2 in* **Paper II***)* (2). A further description of the differences seen between site-based and remote centralized ratings is presented in the appended **Paper II** (2).

INTERRATER AGREEMENT – CENTRALIZED RATERS

ICC comparing ratings from all CR on individual items at the three different assessments are presented in *Table 9 (originally presented as Table 3 in* **Paper II***)* (2).

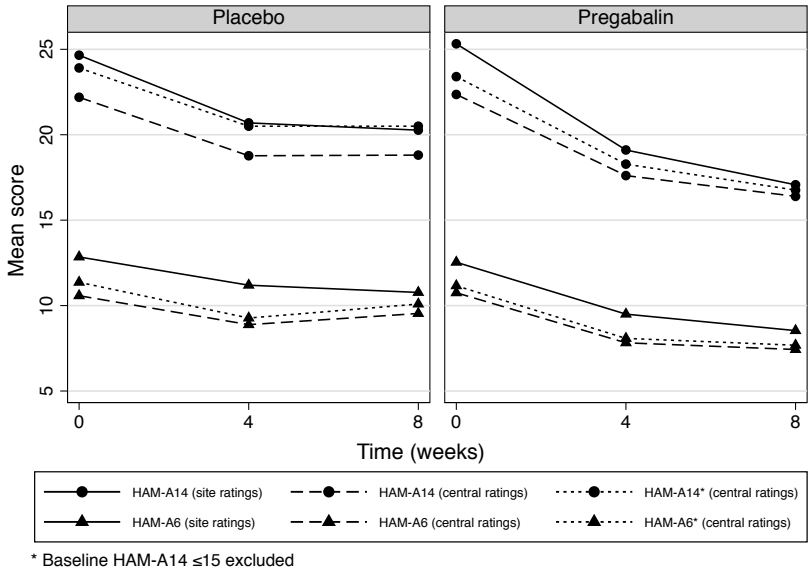

Figure 2 - Difference between site-based and centralized ratings of the HAM scale

Table 1 - Primary outcome measures. ITT analyses of centralized and site-based ratings.

Rating scale and method	Placebo	Pregabalin	Difference after 8 weeks		
	Mean (SD)	Mean (SD)	Mean (95% CI)	Effect size	P
Centralized ratings: All originally included participants, ITT analyses (placebo n=26, pregabalin n=28).					
HAM-A_{14}	22.2 (5.9)	22.4 (4.7)	2.6 (-0.8 to 5.9)	0.42	0.13
HAM-A_6	10.6 (2.8)	10.8 (2.0)	2.3 (0.6 to 4.0)	0.72	0.01
HAM-A (Psychic factor)	12.8 (3.3)	13.0 (3.0)	2.5 (0.1 to 4.5)	0.57	0.04
HAM-A (Somatic factor)	9.5 (3.8)	9.5 (3.1)	0.3 (-1.5 to 2.0)	0.08	0.77
Centralized ratings: Baseline HAM-A_{14} ≤15 excluded, ITT analyses (placebo n=22, pregabalin n=25).					
HAM-A_{14}	23.9 (4.6)	23.4 (3.7)	3.2 (-0.4 to 6.9)	0.50	0.08
HAM-A_6	11.4 (2.0)	10.2 (1.7)	2.2 (0.3 to 4.1)	0.69	0.02
HAM-A (Psychic factor)	13.7 (2.4)	13.6 (2.4)	2.7 (0.0 to 5.3)	0.59	0.05
HAM-A (Somatic factor)	10.4 (3.3)	9.9 (3.1)	0.3 (-1.7 to 2.3)	0.1	0.73
Site-based ratings: All originally included participants, ITT analyses (placebo n=26, pregabalin n=28).					
HAM-A_{14}	24.7 (4.8)	25.3 (4.8)	3.9 (0.3 to 7.4)	0.59	0.03
HAM-A_6	12.8 (2.0)	12.5 (2.2)	1.9 (-0.1 to 3.9)	0.53	0.06
HAM-A (Psychic factor)	15.0 (2.6)	15.0 (3.0)	2.8 (0.3 to 5.3)	0.60	0.03
HAM-A (Somatic factor)	9.6 (3.8)	10.3 (3.7)	1.0 (-1.0 to 3.0)	0.26	0.33

Table 6 - ICC values. Interrater Agreement between individual central raters compared in a two-way mixed effects model on absolute agreement.

	Baseline ratings[1]		4 week ratings[2]		8 week ratings[3]	
HAM Item:	**ICC**	95% CI	**ICC**	95% CI	**ICC**	95% CI
Item 1	0.85	0.76 to 0.91	0.94	0.90 to 0.96	0.93	0.88 to 0.96
Item 2	0.82	0.72 to 0.89	0.92	0.87 to 0.95	0.91	0.85 to 0.95
Item 3	0.85	0.77 to 0.91	0.94	0.90 to 0.96	0.94	0.89 to 0.96
Item 4	0.88	0.81 to 0.93	0.92	0.87 to 0.95	0.90	0.84 to 0.95
Item 5	0.81	0.68 to 0.89	0.86	0.75 to 0.92	0.86	0.76 to 0.92
Item 6	0.95	0.92 to 0.97	0.96	0.93 to 0.98	0.95	0.91 to 0.97
Item 7	0.82	0.72 to 0.89	0.91	0.86 to 0.95	0.90	0.84 to 0.94
Item 8	0.88	0.81 to 0.93	0.88	0.80 to 0.93	0.92	0.85 to 0.96
Item 9	0.89	0.83 to 0.93	0.97	0.96 to 0.98	0.96	0.94 to 0.98
Item 10	0.96	0.94 to 0.98	0.92	0.86 to 0.95	0.97	0.95 to 0.98
Item 11	0.96	0.94 to 0.98	0.96	0.93 to 0.97	0.96	0.94 to 0.98
Item 12	0.89	0.83 to 0.93	0.90	0.83 to 0.94	0.90	0.84 to 0.94
Item 13	0.90	0.85 to 0.94	0.93	0.90 to 0.96	0.93	0.89 to 0.96
Item 14	0.60	0.38 to 0.75	0.58	0.34 to 0.75	0.72	0.55 to 0.84

MOKKEN SCALE ANALYSIS

The coefficients of homogeneity for HAM-A_{14} and HAM-A_6 for both the centralized ratings and site-based ratings, are shown in *Table 10 (originally presented as Table 2 in* **Paper II***)* (2).

Table 7 – Coefficients of homogeneity. Analyses based on ITT data from 8 weeks assessment.

	Coefficient of Homogeneity	
Method of rating	**HAM-A_{14}**	**HAM-A_6**
Centralized Rating	0.30	0.43
Site-based Rating	0.28	0.37

STUDY III

SAMPLE

Baseline characteristics for patients included in **Study III** is presented in *Table 11 (originally presented as Table 1 in* **Paper III***)* (3). Median number of days from baseline assessment to initiation of pregabalin was 5, ranging from 1 to 13 days. Median number of days from initiation of pregabalin to the second assessment was 27 days, ranging from 23 to 32 days, and to the third assessment 56 days, ranging from 51 to 61 days. Further details are provided in the appended **Paper III** (3).

Table 8 - Clinical and treatment characteristics at baseline.

Variable	Placebo group (N=7)		Pregabalin group (N=8)	
	N	%	N	%
Male sex	5	71	4	50
Smokers	3	43	8	100
	Median	Min - Max	Median	Min - Max
Age (years)	50	43 to 52	42	22 to 58
BMI (kg/m^2)	32.5	28.1 to 35.9	27.4	21.1 to 43.5
Plasma creatinine (µmol/L)	86	68 to 103	74	66 to 117
Dosage of clozapine (mg/day)	400	225 to 700	425	150 to 500
Dosage of pregabalin at 4 weeks' assessment (mg/day)	600	150 to 600	450	450 to 600
Dosage of pregabalin at 8 weeks' assessment (mg/day)	600	450 to 600	600	450 to 600

CHANGE IN PLASMA CLOZAPINE

Baseline values and change in plasma clozapine from baseline to the assessments after 4 and 8 weeks of treatment are summarized in *Table 12 (originally presented as Table 2 in* **Paper III***)* (3). The largest individual increase in plasma clozapine

from baseline to 4 weeks assessment was 15% in the pregabalin group and 22% in the placebo group. The largest individual increase from baseline to 8 weeks assessment was 6% in the pregabalin group and 64% in the placebo group.

A graphical presentation of the individual variation in concentration to dose ratio (C/D) over time is shown in *Figure 3 (originally presented as Figure 1 in* **Paper III***)* (3) and boxplots for the assessments in each treatment group is shown in *Figure 4 (Originally presented as Figure 2 in* **Paper III***)* (3). Further details of the change in p-clozapine is presented in the appended **Paper III** (3).

Table 9 - Baseline p-clozapine and absolute change initiation of pregabalin. ([1]Hypothesis testing was made using the Wilcoxon signed-rank test.

Treatment ***- Assessment***	**N**	**Median p-clozapine [ng/mL] (min – max)**	**Median difference from baseline (min – max)**	**Comparison to baseline[1]**
Placebo				
- Baseline	7	*497.8 (153.0 - 1059.8)*	-	-
- 4 weeks	5	*524.8 (138.1 - 765.2)*	*43.4 (-14.9 - 140.3)*	P=0.08
- 8 weeks	7	*488.9 (191.0 - 1082.3)*	*26.9 (-36.0 - 397.4)*	P=0.18
Pregabalin				
- Baseline	8	*516.5 (190.5 - 673.8)*	-	-
- 4 weeks	8	*501.3 (149.8 - 569.0)*	*-29.9 (-179.2 - 72.7)*	P=0.09
- 8 weeks	6	*467.4 (266.1 - 582.6)*	*-102.3 (-236.2 - 14.0)*	P=0.12

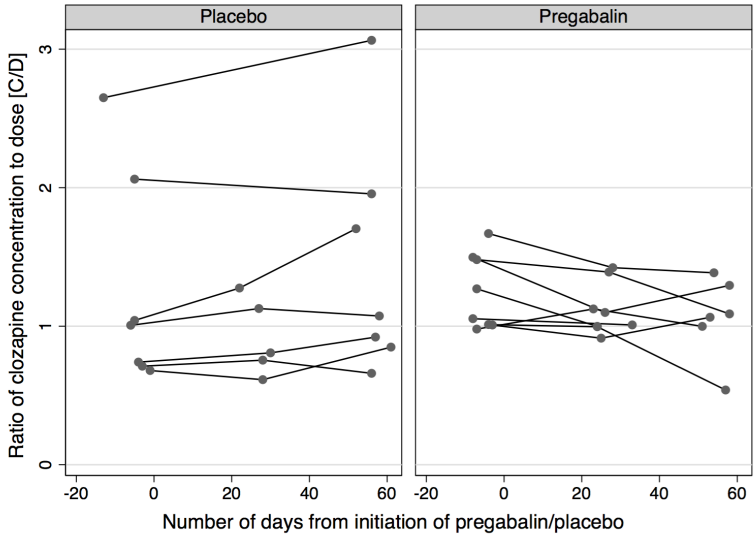

Figure 3 - Graphical presentation of p-clozapine (ng/mL) compared to dose (mg/day), over time

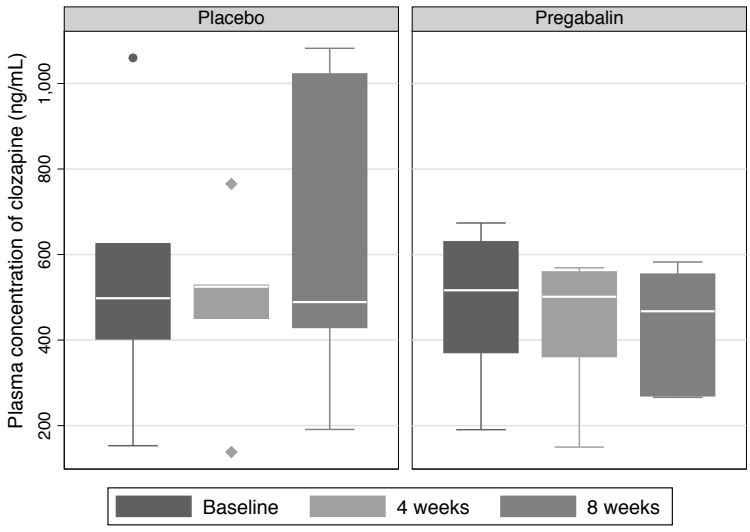

Figure 4 - Box plots of plasma clozapine concentration at baseline and after 4 and 8 weeks of treatment with pregabalin.

STUDY IV

RESULTS FROM LITERATURE SEARCH AND SELECTION PROCESS

Literature search was performed on the 29th of November 2014 (4). No additional data was provided by the Marketing Authorization Holder (4). Selection tree from the literature search is shown in *Figure 5 (Originally presented as Figure 1 in* **Paper IV***) (4)*.

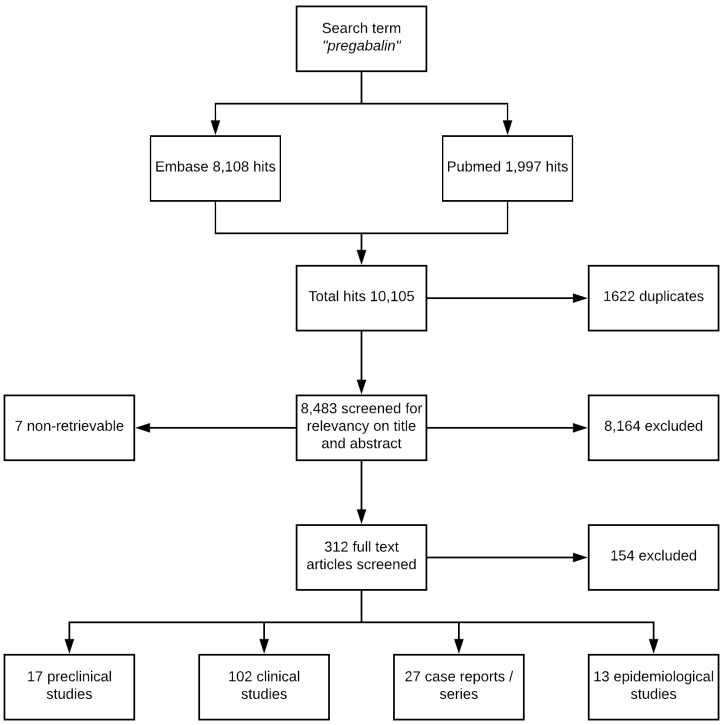

Figure 5 – Selection tree from literature search.

In total 17 preclinical studies were identified – which included seven unpublished studies presented in a FDA report, 102 clinical studies and 13 epidemiological studies. A total of 27 case reports were identified of which misuse and abuse related events were reported in 9 case reports – covering a total of 10 individual patients. The included studies and case reports are presented in brief overview in *Table 1 to 4* in the appended **Paper IV** (4).

7. DISCUSSION

EFFICACY OF PREGABALIN FOR ANXIETY IN SCHIZOPHRENIA

The main topic of this thesis is the evaluation of pregabalin in the treatment of anxiety in patients with schizophrenia. In the PACS study, pregabalin was compared to placebo in patients diagnosed with schizophrenia (1).

Overall, a higher reduction in anxiety symptom severity was seen in the pregabalin group. However, when looking at the full HAM-A_{14} scale this difference was not statistically significant. In the analyses of the subscales of the HAM-A a clinically relevant and statistically significant difference between groups was seen on the HAM-A_6. Studies on GAD have found the HAM-A_6 to cover the core items of anxiety, namely the items of anxious mood, psychic tension, fears, intellectual disturbances, and anxious behavior observed at the interview (43, 80).

Other clinical trials investigating the effect of pregabalin have found effect sizes comparable to those seen in the PACS study (43) and different drugs may have the ability to show effect either on the somatic factor or the psychic factor of the HAM-A scale (102).

Pregabalin is not known to possess antipsychotic effects and in fact, worsening of hallucinations have been associated with treatment of pregabalin (103). In the PACS study, three patients experienced deterioration of hallucinations – all three allocated to treatment with pregabalin (1). However, in a small case series investigating the effect of pregabalin in patients with schizophrenia, a reduction in positive symptom severity on the PANSS scale was found (48). The PANSS scale were used in the PACS study as a secondary efficacy outcome (1). Overall a larger reduction in total PANSS score was found in the pregabalin group. However, as seen in *Table 5*, the largest change was seen on items in the general symptoms subscale and no relevant change was found on the subscales of positive or negative symptoms (1). As a further evaluation was made using the *"five-factor model"* (70) which confirmed that the primary change in PANSS scores was on the items of anxiety specific symptoms (1).

Overall quality of life is lower among persons with schizophrenia compared to the general population (104) and anxiety symptoms impose a negative impact on perceived quality of life (19). Overall quality of life for the participants in the PACS study were found to be comparable to the results founds in a Danish study concerning patients with schizophrenia (104). As seen in *Table* 5, changes in quality of life domains were in favor of pregabalin but only in the domain of *"physical health"* were the difference found to be statistically significant. The short

duration of the PACS study might not be sufficient to detect true changes in quality of life.

Decreased functioning of sleep is a common symptom in anxiety disorders. In the PACS study, sleep functioning was evaluated using the patient rated LSEQ scale. The pregabalin group had a larger change towards better functioning in the *"getting-to-sleep"* domain and, although not statistically significant, in the *"quality-of-sleep"* domain (1). The differences seen between groups might be indicative of the anxiolytic effect of pregabalin but could as well be the result of adverse effects. Somnolence is a frequent adverse effect to pregabalin (105). However, on the VAS scale used for assessment of patient perceived sedation only a small change was seen for the pregabalin group. As presented in Table 6, a notable difference between groups were found in the *"increased duration of sleep"* whereas no relevant difference was found on the *"sedation"* item. Overall, the results indicate that the effect on sleep functioning is not only attributable to the sedative effects of pregabalin.

TOLERABILITY OF PREGABALIN

In the PACS study, overall drop-out rate was lower than expected (1). As shown in *Figure 1*, a total of three patients in the pregabalin group discontinued the study intervention due to suspected adverse effects. Corresponding number for the placebo group was two.

Dizziness is a common adverse effect to treatment with pregabalin (105). Dizziness occurred more frequently in the pregabalin group but the difference between groups were not statistically significant (1). Weight gain, increased duration of sleep and polyuria/polydipsia were significantly also more reported by patients in the pregabalin group compared to the placebo group (1). Weight gain is a critical issue for many patients with schizophrenia and may negatively affect treatment adherence and is associated with lower quality of life (106). The findings in the UKU data was confirmed by the body weight measurements performed at each study visit (1). Eighty-six percent of patients in the pregabalin group experienced weight gain from baseline to end-trial assessment, with a mean weight gain of 2.6 kg, corresponding numbers for the placebo group were 35% and a mean gain of 1.1 kg (1). The findings in the PACS study concerning weight gain is comparable to those reported by Englisch et al. (48). Although definitions are not consistent in literature, a weight change of 7% from baseline weight is often considered as clinically significant (107, 108). Only one patient in the pregabalin group had a weight gain exceeding 7% of baseline weight (1). However, in a study concerning weight changes patterns for patients treated with pregabalin, Cabrera et al found that the majority of patients keep their weight within 7% of baseline weight but

those who gain more weight do so within 2 to 12 months of treatment (108). In the PACS study patients was only followed for 2 months which is a major limitation to the data on weight change (1).

Only a minor and not statistically significant difference was seen between groups on the overall cognitive functioning (1). Mean BACS composite score was slightly increased for the placebo group, supposedly a *"test-retest effect"*, whereas no relevant change was seen for the pregabalin group (1). The difference between groups were not statistically significant and the results from **Study I** indicate that pregabalin does not cause significant impairment in cognitive functioning.

EVALUATION OF HAM-A DATA AND CENTRALIZED RATING

Max Hamilton recommended that a minimum of two raters was used to obtain acceptable precision in the assessment of symptom severity by the HAM-A scale (109). In the PACS study a method of centralized rating was used as a precautionary method of blinding (1, 2). Primary efficacy assessment was based on the combined ratings from all three central raters. As presented in *Table 9*, the interrater reliability between the three central raters was found acceptable supporting that the efficacy assessments were based on the mean rating scores of all three central raters (2).

In **Study II**, a comparison between site-based ratings and centralized ratings was made to evaluate the differences in ratings (2). Interestingly, in the site-based ratings a statistically significant difference between groups was found on the HAM-A_{14} but not on the HAM-A_6 (2). Baseline values for both treatment groups were lower in the centralized ratings compared to the site-based ratings. If eligibility for participation had been assessed by centralized raters seven patients (13%) would not have been included in the study (2). Site-based ratings remained higher than centralized ratings, but the gap was reduced at the assessments after 4 and 8 weeks of treatment (2). As seen in *Figure 2*, this was most clearly seen in the pregabalin group on the HAM-A_{14}.

Statistical comparisons in efficacy trials can be made in several ways. In **Study I** and **Study II**, treatment effect was measured as change from baseline ratings to assessments after 4 and 8 weeks of treatment. This approach considers potential imbalances between treatment groups at baseline but does not correct for the tendency of "regression towards the mean" (110). Patients with a high score at baseline would generally have a higher chance of improvement. Only minor differences in baseline scores was seen in centralized ratings, but a relevant difference was seen in site-based ratings, mostly in the somatic items (2). This might be a part of the explanation for the higher effect size on the somatic anxiety

factor and the HAM-A_{14}, seen in the site-based ratings and not in the centralized ratings.

Generally, substantial loadings were seen on the somatic items of the HAM-A ratings. However, only minor change in these items was seen during treatment (1). This might indicate that pregabalin primarily is effective in treating the psychic component of anxiety in patients with schizophrenia. Another explanation might be adverse effects from concomitant treatment resulted in high loadings on the somatic items and therefore not treatable with pregabalin.

Another factor to consider might be the different psychometric properties of the HAM-A_6 compared to the HAM-A_{14}. A recent study comparing the two versions of the Hamilton depression scale (HAM-D_{17} and HAM-D_6) found a substantial difference between the scales, in their ability show drug superiority compared to placebo (111). Analysis performed in other studies have found the HAM-A_{14} to be multidimensional (43), and have found the HAM-A_6 to have better statistical performance covering the core items for anxiety state severity (43, 74). However, rating scales may perform statistically different depending on the population it is applied to. No previous studies have tested the statistical properties of the HAM-A_{14} and HAM-A_6 in patients with schizophrenia and anxiety symptoms. In **Study II**, a Mokken Scale analysis was performed to measure the scalability of both scales (2). The HAM-A_6 performed better statistically in all assessments (baseline, 4 weeks and 8 weeks) but the highest coefficient of homogeneity was found in the 8 weeks assessment (0.43 for the HAM-A_6 and 0.37 for the HAM-A_{14}) (2). A coefficient of homogeneity from 0.30 to 0.39 is according to Mokken only just acceptable, but levels of 0.40 or higher are quite acceptable (84). These findings indicate a better scalability of the HAM-A_6 compared to the HAM-A_{14} and similar results have previously been reported by Bech (43).

Blinding of treatment allocation in clinical trials is considered fundamental to avoid biased assessments. However, when raters hold knowledge about potential adverse effects experienced by study subjects, functional un-blinding may occur. In **Study II** the blinding success of the PACS study was evaluated using "exit-poll" data collected at the completion of the treatment period for each study participant (2). As shown in *Table 7*, site-based raters were highly able to "guess" treatment allocation for study subjects allocated to placebo. Study subjects were better to "guess" treatment allocation if they had been allocated to pregabalin treatment whereas study subjects guessed almost randomly if they had been allocated to placebo (2). The results concerning blinding of study subjects may both be indicative of participants experience of treatment effect or adverse effects, or may be a result of psychological factors like wishful thinking, i.e. patients want to think they were allocated to the active treatment (99).

The use of end-of-trial assessment of blinding success is a matter of debate (112) and results should be interpreted cautiously (99). However, the results may partly explain some of the differences seen between site-based ratings and the centralized ratings (2). The knowledge about adverse effects might have biased site-based raters distinction between adverse effects and somatic anxiety symptoms – resulting in a larger effect size on the somatic factor of the HAM-A in the site-based ratings and a statistically significant and clinically relevant difference between treatment groups was seen on the $HAM\text{-}A_{14}$.

CLINICAL CONSIDERATIONS TO USE OF PREGABALIN

The suspected DDI interaction between pregabalin and the antipsychotic drug clozapine might impose a limitation to the use of pregabalin in patients with schizophrenia. Englisch and Gahr found a close temporal association between initiation of treatment with pregabalin and increase of plasma clozapine concentration (51, 53). The data from **Study III** provides the largest set of systematic observations addressing the suspected DDI between pregabalin and clozapine (3). Overall, the findings of **Study III** could not support the presence of such DDI as no increase in median p-clozapine in the pregabalin group was found and the largest individual increase was 15% - from baseline to 4 weeks assessment (3). However, studies addressing the intra-individual variation over time have found a significant variation of plasma clozapine on stable dosage of clozapine (113) and several factors have been found to influence the metabolism of clozapine (114). These may be static, like sex, or slowly changing factors like body weight and age, but also more rapidly changing factors like smoking habits or infections influence the metabolism of clozapine (114, 115). As shown in *Figure 3*, the largest individual increase was seen in the placebo group.

An important limitation to the use of pregabalin in patients with schizophrenia is the abuse potential. Assessing abuse potential of a drug is a complex task and although preclinical and epidemiological studies directly have evaluated this topic the overall assessment must be summed up from circumstantial evidence evolved from both preclinical, clinical and epidemiological studies (4). Euphoria is a known adverse effect to the treatment with pregabalin (105).

Based on the review of clinical trials reporting adverse effects euphoria was found to be a transient and dose-dependent adverse effect of pregabalin, occurring independent of indication and previous abuse of substances (4). The feeling of euphoria might explain why some patients tend to overdose pregabalin. As reviewed in **Study IV**, one to ten percent of patients treated with pregabalin experience euphoria as an adverse effect (4). In the PACS study, one patient in the pregabalin group (4%) experienced euphoria, starting at a dosage of 300 mg (1).

Although the feeling of euphoria seems to occur independently of previous substance abuse epidemiological studies have found that high use of pregabalin is more frequent among patients with previous substance abuse (4). These findings were supported by a recent Danish study, which also found an association between the use of antipsychotics with sedative effects and high use of pregabalin (116).

In conclusion, the findings of **Study IV** indicate that pregabalin holds an important abuse potential which is important to consider when prescribing pregabalin, especially for patients with a known history of drug abuse (4). A detailed discussion of the findings of **Study IV** is presented in the appended **Paper IV** (4).

LIMITATIONS AND GENERALIZABILITY

The PACS study did not meet the required sample size and an important limitation to **Study I** and subsequently **Study III** is the low sample size (1, 3). Twenty-five patients were needed in each treatment group to detect a difference between treatment groups of at least 5 points on the total HAM-A_{14} score. The placebo group had a substantial reduction in HAM-A_{14} scores and one of the initial assumptions was that the placebo group would not change (1). Further, the variation in HAM-A scores within the groups were larger than assumed before trial startup (1).

Another factor that may impose limitations to the results are the allowance of concomitant treatment during the PACS study (1). As shown in *Table 3*, a substantial number of patients received treatment with anxiolytic drugs, like antidepressants or hypnotics. However, as concomitant treatment was kept stable for at least four weeks before inclusion and through the study period delayed effects from other drugs are unlikely to have influenced the results (1). The concomitant use of other drugs, may however, in other ways impose a limitation to the results found in this study. Adverse effects may mimic anxiety symptoms, e.g. gastrointestinal adverse effects may be rated as gastrointestinal symptoms of anxiety, akathisia as tension. The presence of adverse effects from concomitant treatment may result in falsely high symptom loadings on the somatic anxiety factor of the HAM-A, which is not reponsive to treatment.

The allowance of concomitant treatment, however, gives higher generalizability. The study sample included in the PACS study is considered close to the population where initiation of treatment with pregabalin would be considered. Many patients were in fact referred when their primary clinician considered treatment with pregabalin as treatment of severe anxiety symptoms. As the study was conducted in an everyday clinical setting, the generalizability of the conclusions are well substantiated.

The HAM-A scale is not originally intended to measure anxiety in schizophrenia (74). However, the only rating scale designed especially for assessment of anxiety in schizophrenia, which is partly based on the HAM-A scale, needs further testing before the clinical and psychometric properties can be evaluated (71). In the PACS study, no sub diagnostic evaluation was made to further characterize anxiety of the included participants (1). It is therefore possible that effect of pregabalin is related to certain profiles of anxiety, and further studies are needed to investigate the nature of anxiety in schizophrenia.

The most important limitation to the conclusions in **Study III** is the small sample size (3). The limited data material does not exclude the possibility that some patients may develop dramatic increases in plasma clozapine when pregabalin is added. The procedures related to the obtainment and handling of blood samples impose further limitations to **Study III** (3). The analyses performed in **Study III** was not originally included in the study design of the PACS study, and the collection of blood samples was not aimed for the investigation of plasma clozapine stability (3). The blood samples used cannot be considered as strict 12h values, as normally requested in assessments of plasma clozapine (117). Within subject variance in clozapine concentration may partly be explained by differences in sampling time between the three assessments (3). Further, blood samples were frozen and stored for later analyses. The storage of blood samples may alter the plasma concentration of clozapine over time. However, median number of days from obtaining blood samples to the analysis was not substantially different between groups (3).

The findings in **Study IV** support the conclusions made in other studies addressing the abuse potential of pregabalin (118-120). The strength **Study IV** is the systematic search strategy and detailed review of the retrieved data. However, as discussed in **Paper IV** (4), bias may have occurred. Most preclinical data originated from studies conducted by the Marketing Authorization Holder (4). Unjustified omission of data from a self-administration study may distort the picture of the preclinical data as data concerning use of pregabalin in high doses were excluded (4). Publication bias may have occurred in relation to published case reports concerning abuse and misuse of pregabalin. Pregabalin was marketed in 2004 but concerns of the abuse potential was first mentioned in published literature several years later (121). Case reports concerning misuse and abuse of pregabalin were not published until 2010 (59, 122, 123). The concerns of abuse potential of pregabalin was solidified in the following years and may have increased the interest for pregabalin in abusive environments but also raised the focus on pregabalin as a drug with abuse potential. Another limitation to **Study IV** is the lack of consistency in the terminology used to describe misuse and abuse related events in the published literature (4).

8. CONCLUSIONS

OVERALL FINDINGS OF THIS THESIS

- Pregabalin was found to be effective, with a moderate effect size, as treatment of anxiety in patients with schizophrenia. The effect, however, was only seen on the psychic anxiety factor of the HAM-A_{14} and on the HAM-A_6. No relevant difference was seen on the somatic anxiety factor. Pregabalin was generally well tolerated and most adverse effects were transient. However, weight gain may be a limiting factor in the use of pregabalin in patients with schizophrenia.
- The method of centralized rating was found to be easy to apply and the overall experience is that this method is applicable in clinical trials using psychometric testing.
- A high interrater agreement between centralized raters supporting the use of mean values in the efficacy assessments in the PACS study. The end-trial assessment of blinding success found signs of functional un-blinding among site-raters. The Mokken Scale Analysis confirmed previous findings suggesting better scalability of the HAM-A_6 than the HAM-A_{14}. Centralized raters were better in separating the effect of pregabalin from placebo on the HAM-A_6 compared to site-based raters.
- In the observational subset of 8 patients from the PACS study, initiation of pregabalin did not increase the plasma concentration of clozapine. These results do not support the suspicion of an underlying drug-drug interaction between clozapine and pregabalin.
- The review of existing literature indicates a relevant abuse potential of pregabalin, which may impose a general limitation to the use of pregabalin. Prescribers should pay attention of signs of abuse, especially in patients with a history of substance abuse.

9. REFERENCES

1. Schjerning O, Damkier P, Lykkegaard SE, Jakobsen KD, Nielsen J. Pregabalin for anxiety in patients with schizophrenia - A randomized, double-blind placebo-controlled study. Schizophr Res. 2017. (Epub ahead of print).
2. Schjerning O, Bech P, Damkier P, Jakobsen KD, Nielsen J. Use of remote centralized rating versus site-based rating in the PACS study. 2018 (manuscript in preparation).
3. Schjerning O, Jakobsen KD, Nielsen J, Damkier P. The effect of pregabalin on plasma levels of clozapine in patients with schizophrenia - results from a randomized trial. 2018 (recommended for publication in Pharmacopsychiatry).
4. Schjerning O, Rosenzweig M, Pottegard A, Damkier P, Nielsen J. Abuse Potential of Pregabalin: A Systematic Review. CNS Drugs. 2016;30:9-25.
5. Uggerby P, Nielsen RE, Correll CU, Nielsen J. Characteristics and predictors of long-term institutionalization in patients with schizophrenia. Schizophr Res. 2011;131:120-6.
6. van Os J, Kapur S. Schizophrenia. Lancet. 2009;374:635-45.
7. Grupe DW, Nitschke JB. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nat Rev Neurosci. 2013;14:488-501.
8. Gross C, Hen R. The developmental origins of anxiety. Nat Rev Neurosci. 2004;5:545-52.
9. Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, et al. Anxiety disorders. Nat Rev Dis Primers. 2017;3:17024.
10. Kraepelin E, Barclay RM, Robertson GM. Dementia praecox and paraphrenia. Edinburgh: Livingstone; 1919.
11. Bosanac P, Castle D. How should we manage anxiety in patients with schizophrenia? Australas Psychiatry. 2015;23:374-7.
12. Achim AM, Maziade M, Raymond E, Olivier D, Merette C, Roy MA. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. Schizophr Bull. 2011;37:811-21.
13. Nebioglu M, Altindag A. The prevalence of comorbid anxiety disorders in outpatients with schizophrenia. Int J Psychiatry Clin Pract. 2009;13:312-7.
14. Bermanzohn PC, Porto L, Arlow PB, Pollack S, Stronger R, Siris SG. Hierarchical diagnosis in chronic schizophrenia: a clinical study of co-occurring syndromes. Schizophr Bull. 2000;26:517-25.
15. Braga RJ, Reynolds GP, Siris SG. Anxiety comorbidity in schizophrenia. Psychiatry Res. 2013;210:1-7.
16. Naidu K, van Staden WC, van der Linde M. Severity of psychotic episodes in predicting concurrent depressive and anxiety features in acute phase schizophrenia. BMC Psychiatry. 2014;14:166.

17. Lysaker PH, Salyers MP. Anxiety symptoms in schizophrenia spectrum disorders: associations with social function, positive and negative symptoms, hope and trauma history. Acta Psychiatr Scand. 2007;116:290-8.
18. Ciapparelli A, Paggini R, Marazziti D, Carmassi C, Bianchi M, Taponecco C, et al. Comorbidity with axis I anxiety disorders in remitted psychotic patients 1 year after hospitalization. CNS Spectr. 2007;12:913-9.
19. Huppert JD, Weiss KA, Lim R, Pratt S, Smith TE. Quality of life in schizophrenia: contributions of anxiety and depression. Schizophr Res. 2001;51:171-80.
20. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28:403-39.
21. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry. 2010;71:839-54.
22. Vulink NC, Figee M, Denys D. Review of atypical antipsychotics in anxiety. Eur Neuropsychopharmacol. 2011;21:429-49.
23. Stern RG, Petti TA, Bopp K, Tobia A. Aripiprazole for the treatment of schizophrenia with co-occurring social anxiety: an open-label cross-taper study. J Clin Psychopharmacol. 2009;29:206-9.
24. Chanachev A, Ansermot N, Crettol Wavre S, Nowotka U, Stamatopoulou ME, Conus P, et al. Addition of aripiprazole to the clozapine may be useful in reducing anxiety in treatment-resistant schizophrenia. Case Rep Psychiatry. 2011;2011:846489.
25. Littrell KH, Petty RG, Hilligoss NM, Kirshner CD, Johnson CG. The effect of olanzapine on anxiety among patients with schizophrenia: preliminary findings. J Clin Psychopharmacol. 2003;23:523-5.
26. Braga RJ, Petrides G, Figueira I. Anxiety disorders in schizophrenia. Compr Psychiatry. 2004;45:460-8.
27. Shinfuku M, Uchida H, Tsutsumi C, Suzuki T, Watanabe K, Kimura Y, et al. How psychotropic polypharmacy in schizophrenia begins: a longitudinal perspective. Pharmacopsychiatry. 2012;45:133-7.
28. Temmingh H, Stein DJ. Anxiety in Patients with Schizophrenia: Epidemiology and Management. CNS Drugs. 2015;29:819.
29. Howells FM, Kingdon DG, Baldwin DS. Current and potential pharmacological and psychosocial interventions for anxiety symptoms and disorders in patients with schizophrenia: structured review. Hum Psychopharmacol. 2017;32. (Epub 2017).
30. Mulholland C, Lynch G, King DJ, Cooper SJ. A double-blind, placebo-controlled trial of sertraline for depressive symptoms in patients with stable, chronic schizophrenia. J Psychopharmacol. 2003;17:107-12.

31. Agarwal V, Agarwal KM. Treatment of obsessive compulsive symptoms in schizophrenia with fluoxetine. Indian J Psychiatry. 2000;42:291-4.
32. Mao YM, Zhang MD. Augmentation with antidepressants in schizophrenia treatment: benefit or risk. Neuropsychiatr Dis Treat. 2015;11:701-13.
33. Novick D, Bousono M, Suarez D, Olivares JM, Montejo AL, Haro JM, et al. Use of concomitant medication with antipsychotic treatment in outpatients with schizophrenia: results from the European Schizophrenia Outpatients Health Outcomes (SOHO) study. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29:972-82.
34. Marco CA, Vaughan J. Emergency management of agitation in schizophrenia. Am J Emerg Med. 2005;23:767-76.
35. Dold M, Li C, Tardy M, Khorsand V, Gillies D, Leucht S. Benzodiazepines for schizophrenia. Cochrane Database Syst Rev. 2012;11:CD006391.
36. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry. 2012;69:476-83.
37. Fontanella CA, Campo JV, Phillips GS, Hiance-Steelesmith DL, Sweeney HA, Tam K, et al. Benzodiazepine use and risk of mortality among patients with schizophrenia: a retrospective longitudinal study. J Clin Psychiatry. 2016;77:661-7.
38. Garay RP, Samalin L, Hameg A, Llorca PM. Investigational drugs for anxiety in patients with schizophrenia. Expert Opin Investig Drugs. 2015;24:507-17.
39. Montgomery S, Emir B, Haswell H, Prieto R. Long-term treatment of anxiety disorders with pregabalin: a 1 year open-label study of safety and tolerability. Curr Med Res Opin. 2013;29:1223-30.
40. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007;73:137-50.
41. Feltner D, Wittchen HU, Kavoussi R, Brock J, Baldinetti F, Pande AC. Long-term efficacy of pregabalin in generalized anxiety disorder. Int Clin Psychopharmacol. 2008;23:18-28.
42. Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry. 2006;67:771-82.
43. Bech P. Dose-response relationship of pregabalin in patients with generalized anxiety disorder. A pooled analysis of four placebo-controlled trials. Pharmacopsychiatry. 2007;40:163-8.
44. Hindmarch I, Trick L, Ridout F. A double-blind, placebo- and positive-internal-controlled (alprazolam) investigation of the cognitive and psychomotor profile of pregabalin in healthy volunteers. Psychopharmacology (Berl). 2005;183:133-43.
45. Oulis P, Konstantakopoulos G. Pregabalin in the treatment of alcohol and benzodiazepines dependence. CNS Neurosci Ther.16:45-50.

46. Swartz MS, Wagner HR, Swanson JW, Stroup TS, McEvoy JP, Canive JM, et al. Substance use in persons with schizophrenia: baseline prevalence and correlates from the NIMH CATIE study. J Nerv Ment Dis. 2006;194:164-72.
47. Schonfeldt-Lecuona C, Wolf RC, Osterfeld ND, Vasic N, Connemann BJ, Schmid M, et al. Pregabalin in the treatment of schizophrenic anxiety. Pharmacopsychiatry. 2009;42:124-5.
48. Englisch S, Esser A, Enning F, Hohmann S, Schanz H, Zink M. Augmentation with pregabalin in schizophrenia. J Clin Psychopharmacol. 2010;30:437-40.
49. Bockbrader HN, Burger P, Knapp L, Corrigan BW. Population pharmacokinetics of pregabalin in healthy subjects and patients with chronic pain or partial seizures. Epilepsia. 2011;52:248-57.
50. Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol. 2003;43:277-83.
51. Englisch S, Alm B, Meyer-Lindenberg A, Zink M. Pregabalin-associated increase of clozapine serum levels. J Clin Psychopharmacol. 2012;32:127.
52. Schjerning O, Lykkegaard S, Damkier P, Nielsen J. Possible drug-drug interaction between pregabalin and clozapine in patients with schizophrenia: clinical perspectives. Pharmacopsychiatry. 2015;48:15-8.
53. Gahr M, Schmid MM, Schönfeldt-Lecuona C. Pregabalin-associated Elevation of Clozapine Serum Levels. Pharmacopsychiatry. 2012;45:297.
54. Nielsen J, Damkier P, Lublin H, Taylor D. Optimizing clozapine treatment. Acta Psychiatr Scand. 2011;123:411-22.
55. Ferslew KE, Hagardorn AN, Harlan GC, McCormick WF. A fatal drug interaction between clozapine and fluoxetine. Journal of forensic sciences. 1998;43:1082-5.
56. Meyer JM, Proctor G, Cummings MA, Dardashti LJ, Stahl SM. Ciprofloxacin and Clozapine: A Potentially Fatal but Underappreciated Interaction. Case reports in psychiatry. 2016;2016:5606098.
57. Halaby A, Kassm SA, Naja WJ. Pregabalin dependence: a case report. Curr Drug Saf. 2015;10:184-6.
58. Grosshans M, Lemenager T, Vollmert C, Kaemmerer N, Schreiner R, Mutschler J, et al. Pregabalin abuse among opiate addicted patients. Eur J Clin Pharmacol. 2013;69:2021-5.
59. Grosshans M, Mutschler J, Hermann D, Klein O, Dressing H, Kiefer F, et al. Pregabalin abuse, dependence, and withdrawal: a case report. Am J Psychiatry. 2010;167:869.
60. Agency EM. Summary of Product Characteristics for Pregabalin http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003880/WC500166172.pdf2014 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003880/WC500166172.pdf.

61. Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikalov A, 3rd, Assuncao-Talbott S. Akathisia: an updated review focusing on second-generation antipsychotics. J Clin Psychiatry. 2009;70:627-43.
62. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry Suppl. 1993:39-44.
63. Addington D, Addington J, Atkinson M. A psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. Schizophr Res. 1996;19:205-12.
64. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261-76.
65. Nicotra E, Casu G, Piras S, Marchese G. On the use of the Positive and Negative Syndrome Scale in randomized clinical trials. Schizophr Res. 2015;165:181-7.
66. Crow TJ. Molecular pathology of schizophrenia: more than one disease process? Br Med J. 1980;280:66-8.
67. Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. Arch Gen Psychiatry. 1982;39:789-94.
68. White L, Harvey PD, Opler L, Lindenmayer JP. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. Psychopathology. 1997;30:263-74.
69. Khan A, Lindenmayer JP, Opler M, Yavorsky C, Rothman B, Lucic L. A new Integrated Negative Symptom structure of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia using item response analysis. Schizophr Res. 2013;150:185-96.
70. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. A new five factor model of schizophrenia. Psychiatr Q. 1994;65:299-322.
71. Llorca PM, Lancon C, Blanc O, de Chazeron I, Samalin L, Caci H, et al. A composite scale applied to evaluate anxiety in schizophrenic patients (SAES). Eur Arch Psychiatry Clin Neurosci. 2014;264:171-8.
72. Hamilton M. Diagnosis and rating of anxiety. Br J Psychiatry. 1969;3(special issue):76-9.
73. Seedat S, Fritelli V, Oosthuizen P, Emsley RA, Stein DJ. Measuring anxiety in patients with schizophrenia. J Nerv Ment Dis. 2007;195:320-4.
74. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50-5.
75. Gjerris A, Bech P, Bojholm S, Bolwig TG, Kramp P, Clemmesen L, et al. The Hamilton Anxiety Scale. Evaluation of homogeneity and inter-observer reliability in patients with depressive disorders. J Affect Disord. 1983;5:163-70.
76. Rickels K, Downing R, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry. 1993;50:884-95.

77. Davidson JR, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. Depress Anxiety. 2004;19:234-40.
78. Allgulander C, Dahl AA, Austin C, Morris PL, Sogaard JA, Fayyad R, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry. 2004;161:1642-9.
79. Portman ME. Generalized anxiety disorder across the lifespan: An integrative approach: Springer Science & Business Media; 2009.
80. Meoni P, Salinas E, Brault Y, Hackett D. Pattern of symptom improvement following treatment with venlafaxine XR in patients with generalized anxiety disorder. J Clin Psychiatry. 2001;62:888-93.
81. Kemp AS, Schooler NR, Kalali AH, Alphs L, Anand R, Awad G, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophr Bull. 2010;36:504-9.
82. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012;200:97-106.
83. Dold M, Kasper S. Increasing placebo response in antipsychotic trials: a clinical perspective. Evid Based Ment Health. 2015;18:77-9.
84. Mokken RJ. A theory and procedure of scale analysis: With applications in political research: Walter de Gruyter; 1971.
85. Greist JH, Mundt JC, Kobak K. Factors contributing to failed trials of new agents: can technology prevent some problems? J Clin Psychiatry. 2002;63 Suppl 2:8-13.
86. Kobak KA, Kane JM, Thase ME, Nierenberg AA. Why do clinical trials fail? The problem of measurement error in clinical trials: time to test new paradigms? J Clin Psychopharmacol. 2007;27:1-5.
87. Williams JB, Kobak KA, Giller E, Reasner DS, Curry L, Detke MJ. Comparison of Site-Based Versus Central Ratings in a Study of Generalized Anxiety Disorder. J Clin Psychopharmacol. 2015;35:654-60.
88. Shen J, Kobak KA, Zhao Y, Alexander MM, Kane JM. Use of remote centralized raters via live 2-way video in a multicenter clinical trial for schizophrenia. J Clin Psychopharmacol. 2008;28:691-3.
89. Bech P. Applied psychometrics in clinical psychiatry: the pharmacopsychometric triangle. Acta Psychiatr Scand. 2009;120:400-9.
90. Hamilton M. Measurement in Psychiatry. In: van Praag HM, Laden MH, Rafaelsen OJ, Sacher E, editors. Handbook of Biological Psychiatry. Part 1. New York: Marcel & Dekker; 1979. p. 85-106.
91. Bech P. Rating scales for psychopathology, health status and quality of life: a compendium on documentation in accordance with the DSM-III-R and WHO systems: Springer Science & Business Media; 2012.

92. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4:28-37.
93. WHOQOL-Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med. 1998;28:551-8.
94. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations - a review. Psychopharmacology (Berl). 1980;71:173-9.
95. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand. 2000;101:323-9.
96. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl. 1987;334:1-100.
97. Barnes TR. The Barnes Akathisia Rating Scale--revisited. J Psychopharmacol. 2003;17:365-70.
98. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 2004;68:283-97.
99. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials. 2004;25:143-56.
100. Bech P. Clinical psychometrics: John Wiley & Sons; 2012.
101. Chen J. BLINDING: Stata module to compute blinding indexes. http://EconPapers.repec.org/RePEc:boc:bocode:s4568982008.
102. Rickels K, Pollack MH, Feltner DE, Lydiard RB, Zimbroff DL, Bielski RJ, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry. 2005;62:1022-30.
103. Olaizola I, Ellger T, Young P, Bosebeck F, Evers S, Kellinghaus C. Pregabalin-associated acute psychosis and epileptiform EEG-changes. Seizure. 2006;15:208-10.
104. Norholm V, Bech P. Quality of life in schizophrenic patients: association with depressive symptoms. Nord J Psychiatry. 2006;60:32-7.
105. Zaccara G, Perucca P, Gangemi PF. The adverse event profile of pregabalin across different disorders: a meta-analysis. Eur J Clin Pharmacol. 2012;68:903-12.
106. Allison DB, Mackell JA, McDonnell DD. The impact of weight gain on quality of life among persons with schizophrenia. Psychiatr Serv. 2003;54:565-7.
107. Verma S, Liew A, Subramaniam M, Poon LY. Effect of treatment on weight gain and metabolic abnormalities in patients with first-episode psychosis. Aust N Z J Psychiatry. 2009;43:812-7.
108. Cabrera J, Emir B, Dills D, Murphy TK, Whalen E, Clair A. Characterizing and understanding body weight patterns in patients treated with pregabalin. Curr Med Res Opin. 2012;28:1027-37.
109. Hamilton M. Lectures on the methodology of clinical research. London: Livingstone; 1961.

110. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ. 2001;323:1123-4.
111. Ostergaard SD, Bech P, Miskowiak KW. Fewer study participants needed to demonstrate superior antidepressant efficacy when using the Hamilton melancholia subscale (HAM-D6) as outcome measure. J Affect Disord. 2016;190:842-5.
112. Henneicke-von Zepelin HH. Assessment of blinding in clinical trials. Contemp Clin Trials. 2005;26:512; author reply 4-5.
113. Kurz M, Hummer M, Kemmler G, Kurzthaler I, Saria A, Fleischhacker WW. Long-term pharmacokinetics of clozapine. Br J Psychiatry. 1998;173:341-4.
114. Haring C, Fleischhacker WW, Schett P, Humpel C, Barnas C, Saria A. Influence of patient-related variables on clozapine plasma levels. Am J Psychiatry. 1990;147:1471-5.
115. Clark SR, Warren NS, Kim G, Jankowiak D, Schubert KO, Kisely S, et al. Elevated clozapine levels associated with infection: A systematic review. Schizophr Res. 2018;192:50.
116. Schjerning O, Pottegard A, Damkier P, Rosenzweig M, Nielsen J. Use of Pregabalin - A Nationwide Pharmacoepidemiological Drug Utilization Study with Focus on Abuse Potential. Pharmacopsychiatry. 2016;49:155-61.
117. Jakobsen MI, Larsen JR, Svensson CK, Johansen SS, Linnet K, Nielsen J, et al. The significance of sampling time in therapeutic drug monitoring of clozapine. Acta Psychiatr Scand. 2017;135:159-69.
118. Bramness JG. [Abuse of pregabalin]. Tidsskr Nor Laegeforen. 2010;130(17):1703-4.
119. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs. 2014;28:491-6.
120. Papazisis G, Tzachanis D. Pregabalin's abuse potential: a mini review focusing on the pharmacological profile. Int J Clin Pharmacol Ther. 2014;52:709-16.
121. Chalabianloo F, Schjott J. [Pregabalin and its potential for abuse]. Tidsskr Nor Laegeforen. 2009;129:186-7.
122. Filipetto FA, Zipp CP, Coren JS. Potential for pregabalin abuse or diversion after past drug-seeking behavior. J Am Osteopath Assoc. 2010;110:605-7.
123. Westin AA, Strom EJ. [Yes, pregabalin can be abused!]. Tidsskr Nor Laegeforen. 2010;130:2108.

10. APPENDIX I - IV

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